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Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Prognostic and Predictive Factors



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Prognostic and Predictive Factors

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Jackisch / Nitz / Kreipe

Data bases screened

Pubmed 2008 - 2021, ASCO 2017-2021, SABCS 2003 – 2021, ESMO 2021, Cochrane data base (n.d.)



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Definition

A Prognostic Factors is associated with the probability of the course of the disease (e.g. disease-free or progression-free survival, overall survival). The probability can be influenced by therapy.

A Predictive Factor is associated with the probability of the effect of a given therapy.

Definition of Prognosis and Prediction

1. Hayes DF, Bast RC, Desch CE et al.:Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. J Natl Cancer Inst. 1996 Oct 16;88(20):1456-66.
2. McGuire WL, Clark GM. Prognostic factors and treatment decisions in axillary-node-negative breast cancer. N Engl J Med. 1992 Jun 25;326(26):1756-61.

The slide is a presentation slide with a light gray background. In the top left corner, there is a logo for AGO (Arbeitsgemeinschaft Gynäkologische Onkologie) and a smaller logo for MAMMA. Below these logos, the text reads: '© AGO e. V. in der DGGG e. V. sowie in der DKG e. V. Guidelines Breast Version 2022.1E'. At the bottom left, the website 'www.ago-online.de' is listed, followed by the motto 'FORSCHEN LEHREN HEILEN'. The main title of the slide is '“Low absolute risk implies low absolute benefit”' in a large, bold, black font. At the bottom right, the source is cited: 'Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Lancet 379: 432-444, 2012'.

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**“Low absolute risk implies
low absolute benefit”**

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

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Lancet 379: 432-444, 2012
2. Peto, R., Davies, C., Godwin, J., et al. 2012. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 379, 432–444.
3. Nielsen T, Jensen B, et al High risk premenopausal luminal A breast cancer patients derive no benefit from adjuvant chemotherapy: results from DBCG77B, SABCS 2015S1-08



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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

1. Febbo PG, Ladanyi M, Aldape KD, et al. (2011) NCCN Task Force report: Evaluating the clinical utility of tumor markers in oncology. J Natl Compr Canc Netw 9 Suppl 5: S1-32; quiz S33.
2. Hayes DF, Bast RC, Desch CE et al. (1996) Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. J. Natl. Cancer Inst. 88 (20): 1456–1466.
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4. Jeremy Howick, Iain Chalmers, Paul Glasziou, et al. Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (Background Document). Oxford Centre for Evidence-Based Medicine.
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7. Simon RM, Paik S, Hayes DF (2009) Use of archived specimens in evaluation of prognostic and predictive biomarkers. J. Natl. Cancer Inst. 101 (21): 1446–1452.

Early Breast Cancer (M0) – eBC Prognostic Factors I			
Factor	Oxford		
	LoE _{Ox2001}	GR	AGO
▪ Tumor size - pT	1a	A	++
▪ Axillary lymph node status - pN	1a	A	++
▪ Histological tumor type (mucinous, tubular etc.)	2b	B	++
▪ Grade (Elston & Ellis) - G	2a	B	++
▪ Age	2a	B	++
▪ Histologically proven peritumoral lymphatic vessel and vascular invasion (L1 V1)	1b	B	++
▪ pCR after NACT* in (luminal-B-like, HER2+, TN)	1a	A	++
▪ Increased risk of recurrence in invasive-lobular BC, cT3/4, N+	2a	B	+/-
▪ Obesity (BMI > 30 kg/m ²)	1b	B	+
▪ Margins (resection status) - R0 / R1	1a	A	+

* NACT = Neoadjuvant Chemotherapy

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2. Harris LN, Ismaila N, McShane LM et al.: Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2016 Apr 1;34(10):1134-50.
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4. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol. 2015 Aug;26(8):1533-46.

Tumor size

1. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol. 2015 Aug;26(8):1533-46.
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Lymph node status

1. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol.* 2015 Aug;26(8):1533-46.
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Histological type (mucinous, tubular etc.)

1. Dieci MV, Orvieto E, Dominici M. Rare breast cancer subtypes: histological, molecular, and clinical peculiarities. *Oncologist.* 2014 Aug;19(8):805-13.
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Tumor grade (Elston & Ellis)

1. Thomas JS, Kerr GR, Jack WJ et al. Histological grading of invasive breast carcinoma--a simplification of existing methods in a large conservation series with long-term follow-up. *Histopathology.* 2009 Dec;55(6):724-31.
2. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol.* 2015 Aug;26(8):1533-46.
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Age

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3. Brandt J, Garne JP, Tengrup I et al. Age at diagnosis in relation to survival following breast cancer: a cohort study. *World J Surg Oncol*. 2015 Feb 7;13:33.

Histologically proven lymph and/or blood vessel invasion

1. Ryu YJ, Kang SJ, Cho JS et al. Lymphovascular invasion can be better than pathologic complete response to predict prognosis in breast cancer treated with neoadjuvant chemotherapy. *Medicine (Baltimore)*. 2018 Jul;97(30):e11647

pCR after NACT* in Luminal B-like, HER2 and TN Breast Cancer

1. Nekljudova V, Loibl S, von Minckwitz G et al. Trial-level prediction of long-term outcome based on pathologic complete response (pCR) after neoadjuvant chemotherapy for early-stage breast cancer (EBC). *Contemp Clin Trials*. 2018 Aug;71:194-198.
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Increased risk of recurrence in invasive-lobular BC, cT3/4, N+

1. Huober J, Schneeweiss A, Blohmer J-U, et al. Factors predicting relapse in early breast cancer patients with a pathological complete response after neoadjuvant therapy – Results of a pooled analysis based on the GBG meta-database, SABCS 2018; P2-08-01
2. Thomas M, Kelly ED, Abraham J et al. Invasive lobular breast cancer: A review of pathogenesis, diagnosis, management, and future directions of early stage disease. *Semin Oncol*. 2019 Apr;46(2):121-132.

Obesity (BMI > 30 kg/m²)

1. Chan DSM et al. Body mass index and survival in women with breast cancer—systematic literature review and meta-analysis of 82 follow-up studies *Ann Oncol*. Oct 2014; 25(10): 1901–1914.
2. Xia X, Chen W, Li J et al. Body mass index and risk of breast cancer: a nonlinear dose-response meta-analysis of prospective studies. *Sci Rep*. 2014 Dec 15;4:7480.
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treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol, 2014. 21(3): p. 717-30.

Resection status (R0 / R1)

1. Harris LN, Ismaila N, McShane LM et al.: Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2016 Apr 1;34(10):1134-50.
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Early Breast Cancer (M0) - eBC Prognostic Factors II			
Factor	Oxford		
	LoE	GR	AGO
▪ ER / PR	1a	A	++
▪ HER2 (IHC, ISH)	1a	A	++
▪ ER / PR / HER2/ Ki-67 to assess the intrinsic type with regards to tumor histology and biology	2b	B	++
▪ uPA / PAI-1 (Femtele® ELISA) in N0	1a	A	+
▪ Proliferation markers			
▪ Ki-67 before, during, or after treatment	1a	B	+
▪ Ki-67 Re-Evaluation after short term preoperative endocrine therapy (2-4 weeks) (ypT and ypN)*	1a	B	+

* Biomarker and Multi Gene Expression test should be evaluated on core needle biopsy prior endocrine therapy

ER/PR

1. Allison KH, Hammond MEH, Dowsett M et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. *J Clin Oncol*. 2020 Jan 13;JCO1902309 (und: *Arch Pathol Lab Med*. 2020 Jan 13).
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HER2

1. Ross, J.S., Slodkowska, E.A., Symmans, W.F., et al. 2009. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *Oncologist* 14, 320–368.
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uPA/PAI-1

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Ki-67

1. Cheang, M.C.U., Chia, S.K., Voduc, D. et al.: 2009. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. *J. Natl. Cancer Inst.* 101, 736–750. doi:10.1093/jnci/djp082.
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Post-treatment Ki-67

1. Dowsett M, Smith IE, Ebbs SR, et al: Prognostic Value of Ki67 Expression After Short-Term Presurgical Endocrine Therapy for Primary Breast Cancer. *Journal of the National Cancer Institute* 99:167-170, 2007
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Reproducibility – Quality Assurance is Key for Clinical Decision Making

- **ER / PR: concordance** central vs local is high (97%; Plan B, SABCS 2014)
- **Grade: 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: grade 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)
- **Ki67:**
 - Inter- and intraobserver variability in measurement of Ki-67 is high (J Nat. Cancer Institute 2011)
 - High reproducibility for low and high Ki67 levels (J Pathol 2002)
 - Standardized methodology improves analytical validity (JNCI 2020)

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Early Breast Cancer (M0) - eBC Prognostic Factors III			
Factor	Oxford		
	LoE	GR	AGO
■ Gene expression profiles (GEP, multigene assays, gene signatures)			
■ MammaPrint® (N0-1)	1b	A	++
■ Oncotype DX® (N0-1, HR+ HER2-)	1b	A	++
■ EndoPredict® (N0-1, HR+, HER2 -)	2b	B	++
■ Prosigna® (N0-1, HR+, HER2 -)	2b	B	++
■ Breast Cancer Index SM (N0-1, HR+ HER2-)**	2b	B	+/-*
■ IHC4 (ER / PR / HER2 / Ki-67)	2b	B	+/-
■ PREDICT® algorithm (https://breast.predict.nhs.uk/)	1b	A	+
■ Clinical-pathological score for lobular breast cancer (nodal status, tumor size, lymphovascular invasion LVI)	2b	B	+/-
■ CTSS Clinical Treatment Score**	2b	B	+
■ CPS-EG Score	2b	B	+

* Should only be used in the context of clinical-pathological criteria (tumor size, nodal involvement, grade, Ki-67, ER, PR, HER2)
 ** Estimation of late recurrence

Gene expression profiles (GEP; Multigene Assays, Gene expression signatures)

(*Should only be used in the context of clinico-pathological criteria (e.g. tumor size, number involved lymph nodes, grade, Ki67) for therapeutic decision making)

MammaPrint®

1. Slambrouck L, Darrigues L, Laurent C et al. Decentralization of Next-Generation RNA Sequencing-Based MammaPrint® and Blueprint® Kit at University Hospitals Leuven and Curie Institute Paris. Transl Oncol. 2019 Dec;12(12):1557-1565.
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Early Breast Cancer (M0) - eBC Prognostic Factors IV			
Factor	Oxford		
	LoE	GR	AGO
▪ Disseminated tumor cells (DTC, in bone marrow)	1a	A	+/-
▪ Circulating tumor cells (CTC, in blood, Cell Search®)*	1b	A	+/-
▪ CTC before NACT (regarding OS, DDFS, LRFI)	1b	B	+/-
▪ Therapy decisions based on CTC phenotypes	3a	C	-
▪ Cell-free DNA (cfDNA, in blood, for DFS, PFS, OS)	2b ^a	B	+/-

* 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®) §	Breast Cancer Index® (BCI) §
Provider	Agendia	Genomic Health	Sividon (Myriad)	NanoString	Biotheranostics
Type of assay	70-gene assay	21-gene recurrence score	11-gene assay	50-gene assay	5 + 2 (MGI+H/I)
Type of tissue	fresh frozen (technical validation for FFPE available)	FFPE	FFPE	FFPE	FFPE
Technique	Microarrays for RNA	qRT-PCR	q-RT-PCR	Direct hybridization (NanoString)	q-RT-PCR
Central lab	yes	yes	no	no	yes
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	Prognostic pT1-3pNo – pN1 ER+ / HER2- Endocrine treated
Risk classes	Low – high	RS (Low – intermediate – high)	Low – high	ROR (Low – inter- mediate – high), molecular types	Low - high
Clinical Validation	Yes	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	Service Mark (SM)

§ 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®) §	Breast Cancer Index® (BCI)
Prognosis after 5 yrs (late recurrences)	not separately shown	yes	yes	yes	yes
Predictive impact (chemotherapy benefit)	poorly validated	yes	not shown	not shown	EAT after 5 yrs
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%)	TransATTOM (11%)
Prospective evidence	MINDACT (N0, N1) (8y DFS, OS)	TAILORx (9y DFS, OS), N0, RS≤25 vs. ≥26 PlanB (N0 highrisk/N+) (5y DFS, OS) RxPONDER (5y DFS, OS), N1, RS≤25 vs. ≥26 ADAPT (5y DFS, OS), N0-1, RS 0-11; RS12- 25/Ki67 response	–	–	–

§ Validated clinical data only available for this assay

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AGOSTADENPROSCHAFT
ONKOPROFESSORIN
FÜR GYNEKOLOGIE UND
MAMMA

Prospective Clinical Trials (Oncotype DX® [TAILORx, PlanB, RxPONDER, ADAPT], MammaPrint® [MINDACT])

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Guidelines Breast
Version 2022.1E

Prognosis in low-risk groups excellent for both tests: ~ 94% 5 J. DFS with only adjuvant endocrine therapy (ET)

	TailorX	RxPONDER	PlanB	ADAPT	MINDACT
Follow-up	Median 90 months	Median 5.1 years	5-J-DFS	Median 60 months	Median 8.7 years (ASCO 2020)
Trial design (biomarker question)	pN0; Randomization RS 11-25 (+/- CTX)	pN1; Randomization RS0-25 (+/- CTX)	Prospective ODX testing: ET alone in RS 0-11 pN0-1	Non-inferiority (iDFS) ET alone: RS 0-11 vs. RS12-25/ET response	Prospectively defined 5y-DMFS threshold for ET alone
Percentage clinically defined low-risk group	6615/9427 (70.2%, adj-online)	all 1-3 involved lymph nodes	all clinical CTX indication (pN0-1)	all clinical chemotherapy (CTX) indication (c/pN0-1)	3336/ 6693 (49.8%, adj-online)
Percentage high clinical risk and low genomic risk (clinical CTX indication)	16.7% (RS 0-10)	42.8% (RS 0-13)	15.3% (RS 0-11)	ET-trial (pN0-1): all RS 0-25, i.e. low genomic risk with ET alone	23.2% (high clinical/low genomic risk)
Test failure rate	n.r.	n.r.	2.9%	n.r.	26% (fresh frozen)
Percentage genomically intermediate-risk group (only for Oncotype DX, ODX)	69.1% (RS 11-25)	57.2% (RS 14-24)	60.4% (RS 12-25)	Included only RS 0-11 (37.9%) or RS 12-25/ET response (62.1%)	n.a.
Percentage genomically high-risk group (only for Oncotype DX)	14.3% (RS ≥ 26)	n.a.	24.3% (RS ≥ 26)	n.a.	27.0% (high clinical <u>and</u> high genomic risk)
10-year follow-up	n.r.	n.r.	n.r.	n.r.	n.r.

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Mammaprint

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Oncotype DX

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Adjuvant Endocrine Therapy Predictive Factors for DFS				
Therapy	Factor	Oxford		
		LoE	GR	AGO
Endocrine therapy	ER / PR status [%]	1a	A	++
	IHC staining intensity (ER/PR)	1a	A	-
	KI-67 Re-Evaluation after short preoperative endocrine therapy (2-4 weeks) (ypT and ypN)*	1b	A	+
Extended endocrine therapy (EAT)	Breast Cancer Index SM (5 yrs. Let (MA.17) or 5 yrs. Tam (aTTOM), resp., after 5 yrs. Tam)	2b	B	+
Tamoxifen	CYP2D6-polymorphism	2b	B	-
Ovarian ablation or suppression	Menopausal status	1c	A	++
Aromatase inhibitors vs. tamoxifen	Menopausal status	1c	A	++
	ER / PR / HER2 as single factors	1c	A	-
	Invasiv-lobular breast cancer	2b	B	+
	KI-67 high	2b	B	+/-
	Obesity (BMI > 30 kg/m ²)	2b	B	+/-

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Adjuvant Chemotherapy and Targeted Therapy Predictive Factors for DFS				
Therapy	Factor	Oxford		
		LoE	GR	AGO
■ Adjuvant Chemotherapy	uPA / PAI-1 (ELISA, Femtelle®)	1a	A	+/-
	70-Gene-signature (Mammaprint®)	1b	A	+
	21-Gene-signature (Oncotype DX RS®)	1b	A	+
	EPclin (Endopredict®)	2b	B	+
	PAM-50 (Prosigna®)	2b	B	+
	Histological type (lobular vs. NST)	2b	B	-
	TIL's in TNBC	2b	B	+/-
■ Anti-HER2-Therapy	HER2 (IHC, ISH)	1a	A	++
■ PARP-Inhibitors	gBRCA1/Mutation (HER2 neg.)	1a	A	+

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see evidence in chapter “Chemotherapy and targeted therapy”

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<div>  <h2>Entscheidungshilfe prospektiv evaluierter Biomarker (LOE1a) und Therapieoptionen (eBC)</h2> </div>		
<div> <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2022.1E</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p> </div>	Biomarker/ Signatur	Subtyp/ Population
	MammaPrint (MINDACT)	HR+ / HER2- N0 N1
	Oncotype DX (TAILORx, RxPonder)	HR+ / HER2- N0 N1
	RS + postendokrines Ki – 67 (ADAPT)	HR+ / HER2- N0 N1
	gBRCA1/2 Mutation (Olympia)	HER2- Stad II/III TN ≥ pT2 oder ≥ HR+, > 4 + LK
Therapieoption		
Postmenopausal, HR+:		
Bei low risk MammaPrint keine adjuvante CHT Indikation		
Bei N0 / RS ≤ 25 keine adjuvante CHT Indikation		
Bei N1 / RS ≤ 25 keine adjuvante CHT Indikation (Postmenopause)		
Identisch zu TAILORx/RxPonder		
Endokrine Monotherapie:		
- Prämenopause bei RS ≤ 11		
- RS 12-25/niedriges klinisches Risiko/Ki 67 post < 10 %		
1 Jahr Olaparib 300 mg 2 x tägl.		

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PARPi

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Neoadjuvant Systemic Chemotherapy (NACT) Predictive Factors for pCR I				
Factor	pCR* Probability	Oxford		
		LoE	GR	AGO
▪ Young age	↑	1a	A	+
▪ Obesity	↓	2a	B	+
▪ cT1 / cT2 tumors o. N0 o. G3	↑↑	1a	A	++
▪ Negative hormone receptor status	↑↑	1a	A	++
▪ Triple negative breast cancer	↑↑	1a	A	++
▪ Positive HER2-status	↑↑	1a	A	++
▪ Early clinical response	↑	1b	A	+
▪ Lobular tumor type	↓	1a	A	+
▪ Metaplastic tumor type	↓↓	4	C	+

* High (↑) or very high (↑↑) probability to reach pCR, low (↓) or very low (↓↓) probability to reach pCR
See also chapter „Prognostic and predictive factors“

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Neoadjuvant Systemic Chemotherapy (NACT)				
Predictive Factors for pCR II				
Factor	pCR* Probability	Oxford		
		LoE	GR	AGO
▪ Gene expression profiles (gene signatures) (Mammaprint®, Endopredict®, Oncotype DX®, Prosigna®, Breast Cancer Index SM)	↑	2b	B	+/-
▪ Ki-67	↑	2b	B	+
▪ Tumor infiltrating lymphocytes**	↑	2a	B	+
▪ PIK3CA mutation (for HER2-positive BC)	↑	2a	B	+/-
▪ gBRCA-mutation (for the effect of chemotherapy)	↑	2b	B	+
▪ gBRCA-mutation (for the effect of platinum)	↔	2b	B	+/-

* High (↑) or very high (↑↑) probability of pCR, low (↓) or very low (↓↓) probability of pCR

** 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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Metastatic Breast Cancer (mBC) Prognostic Factors			
Factor	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Circulating tumor cells (CTC in blood, Cell Search®) <ul style="list-style-type: none"> Prognosis Early response assessment (3w) Therapy decision solely based on dynamics of CTC numbers over time or CTC phenotype Cell-free DNA (cfDNA in blood) 	 1a 1b 1b 2a	 A B A A	 + + -* +/-
* Study participation recommended			

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Treatment of Metastatic Breast Cancer				
Predictive Factors for response				
Therapy	Factor	Oxford		
		LoE	GR	AGO
▪ Endocrine therapy	ER / PR (prim. tumor, better: metastasis)	1a	A	++
	Response to prior therapy	2b	B	++
	Autocrine receptor mutation (ESR1)	2b	B	+
▪ Alpelisib	PIK3CA mutation (prim. tumor, metastases, plasma)	1b	A	++
▪ Chemotherapy	Response to prior therapy	1b	A	++
▪ Anti-HER2-therapy	HER2 (prim. tumor, better: metastasis)	1a	A	++
▪ Checkpoint-inhibitors	PD-L1 positivity [#] (PD-L1c, CPS) in TNBC (primary tumor or metastasis)	1b	B	++
▪ PARP-Inhibitors	gBRCA1/2-mutation	1a	A	++
▪ Bone modifying drugs	Bone metastasis	1a	A	++
▪ Further therapies	CTC monitoring	1b	A	+*

* In clinical trials; # see chapter „pathology“

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 Mutation Diagnostics* in mBC: „Precision Medicine“ for Targeted Therapies							
Altered genes	Therapeutic relevance	Gene region	Material	Oxford			
				LOE	GR	AGO	
BRCA1, BRCA2	PARP-Inhibitors	All exons	Germline: Blood cells	1b	A	++	
			Somatic: Tissue	2b	B	+/-	
PALB2	PARP-Inhibitors	Exons 7, 9 and 20	Germline: Blood cells	2b	B	+	
PIK3CA	Alpelisib		Primary tumor, metastases, plasma	1b	A	++	
HER2-mutation (independent of HER2-status)	Neratinib, lapatinib	Kinase- and extracellular domains; S310, L755, V777, Y772_A775dup	Primary tumor, metastases, plasma particul. lobular BC	4	C	+/-	
ESR1	Resistance against AI	Exons 4, 7 and 8	Metastases, plasma	2b	B	+/-	
NTRK gene fusion	Larotrectinib, entrectinib	Fusion- and splice variants	Tumor tissue, particul. secretory breast cancer	2a	B	+	
MSI	Pembrolizumab	Microsatellite-instability	Tissue	2a	B	+	
* Ideally panel diagnostics							

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BRCA 1/2:

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FDA approval across tumor entities (23.5.17): see full prescribing information for pembrolizumab

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 Decision guidance prospectively evaluated biomarkers (LOE1a) and therapy options (mBC)		
 © AGO e. V. in der DGGG e.V. sowie in der DKG e.V. Guidelines Breast Version 2022.1E www.ago-online.de FORSCHEN LEHREN HELEN	Biomarker / Signature-therapy option	Subtyp / Population
	PDL-L1 $\geq 1\%$	TN
	CPS > 10	TN
	PIK3CA mutation	HR+ / HER2-
		Therapy option
		First line Atezolizumab + nab Paclitaxel
		First line Pembro + chemotherapy
		Fulvestrant + Alplisib after failure of first line ET
		Olaparib, Talazoparib

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Therapy-Relevant Mutational Analysis for „Actionable“ Genomic Alterations in BC

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Diagnostic Tool*	Outcome	Oxford			AGO
		LoE	GR		
Evidence from studies with other cancer patients („tumor-agnostic testing“)					
▪ Companion Diagnostics for therapies of other tumor entities (e.g. BRAF, FGFR1, ...)	Efficacy of diverse therapies	4	D		+/-**
▪ Large Panel Gene Analysis (e.g. FoundationOne, GPS Cancer, NeoSelect, Molecular Health Guide, local „hand-selected„ panels)	Efficacy of diverse therapies, prognosis	3a	C		+/-**
▪ Next Generation Sequencing (NGS) (recommended only in Tier 1 + 2)	Efficacy of evaluated drugs	1b	B		+/-**

- * Assessment method for somatic mutations (tumor tissue, cf-DNA) is not taken into consideration for LoE
- ** Participation in clinical trials or structured registries recommended

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Joint Consensus Recommendations of AMP, ACMG, ASCO and CAP for Reporting Genetic Variants in Cancer

Tier	LoE	Explanation
Tier 1	A.1	Biomarkers that predict response or resistance to FDA-approved therapies for a specific type of cancer
	A.2	Biomarkers included in professional guidelines that predict response to therapies for a specific type of tumor
	B	Biomarkers that predict response or resistance to therapies for a specific type of tumor based on well-powered studies with consensus from experts in the field
Tier 2	C.1	Biomarkers that predict response or resistance to therapies approved by the FDA or professional societies for a different type of tumor
	C.2	Biomarkers that serve as inclusion criteria for clinical trials
	D	Biomarkers that show plausible therapeutic significance based on preclinical studies
Tier 3	Not observed at a significant allele frequency in the general or specific subpopulation databases, or pan-cancer or tumor-specific variant databases. No convincing published evidence or cancer association	
Tier 4	Observed at significant allele frequency in the general or specific subpopulation Databases. No existing published evidence of cancer association	

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Treatment Recommendations for genetic variants

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