Guidelines Breast
Version 2021.1E

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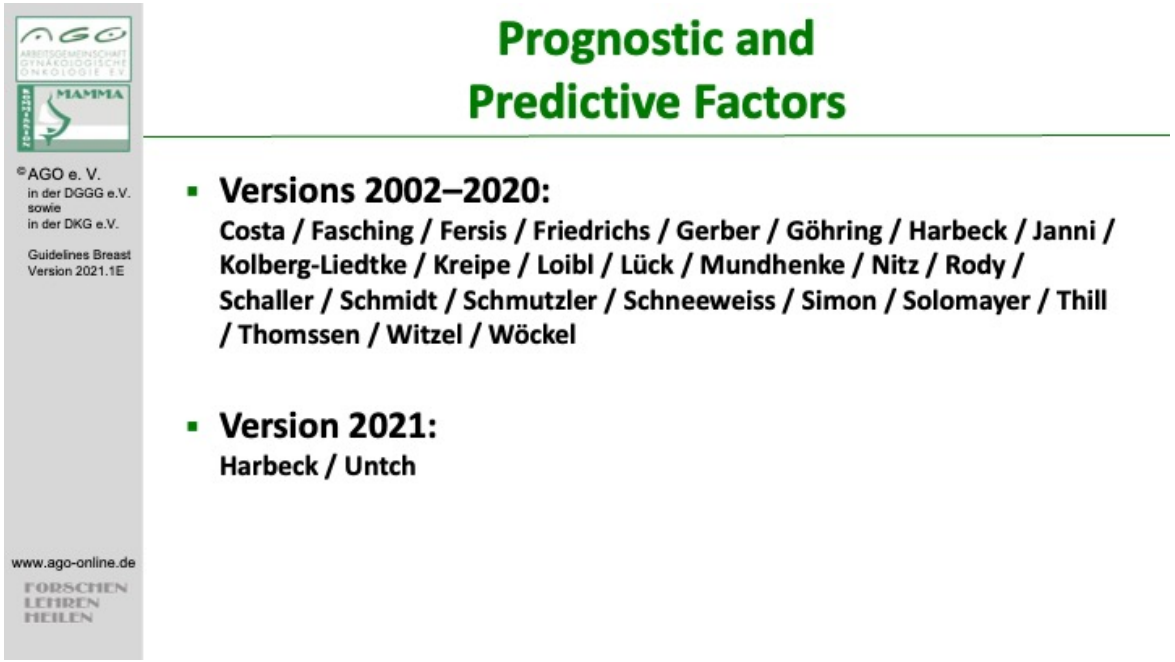
Prognostic and Predictive Factors



Data bases screened

Pubmed 2008 - 2012, ASCO 2003 – 2012, SABCS 2003 – 2012, Cochrane data base (n.d.)

Guidelines screened

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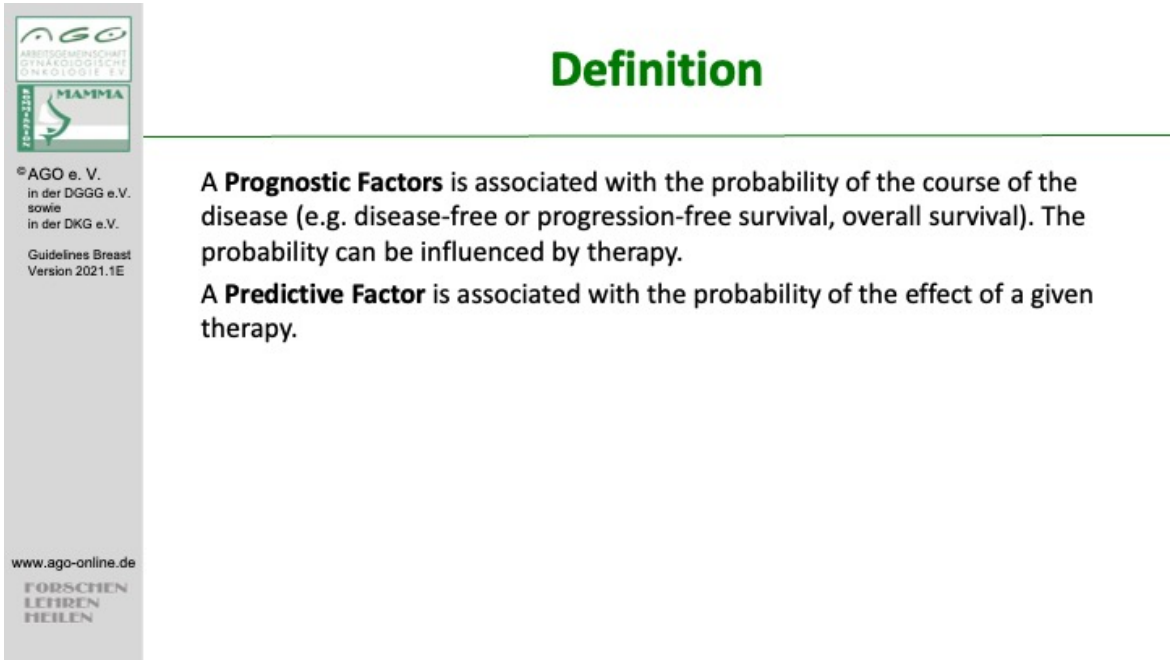

Definition of Prognosis and Prediction

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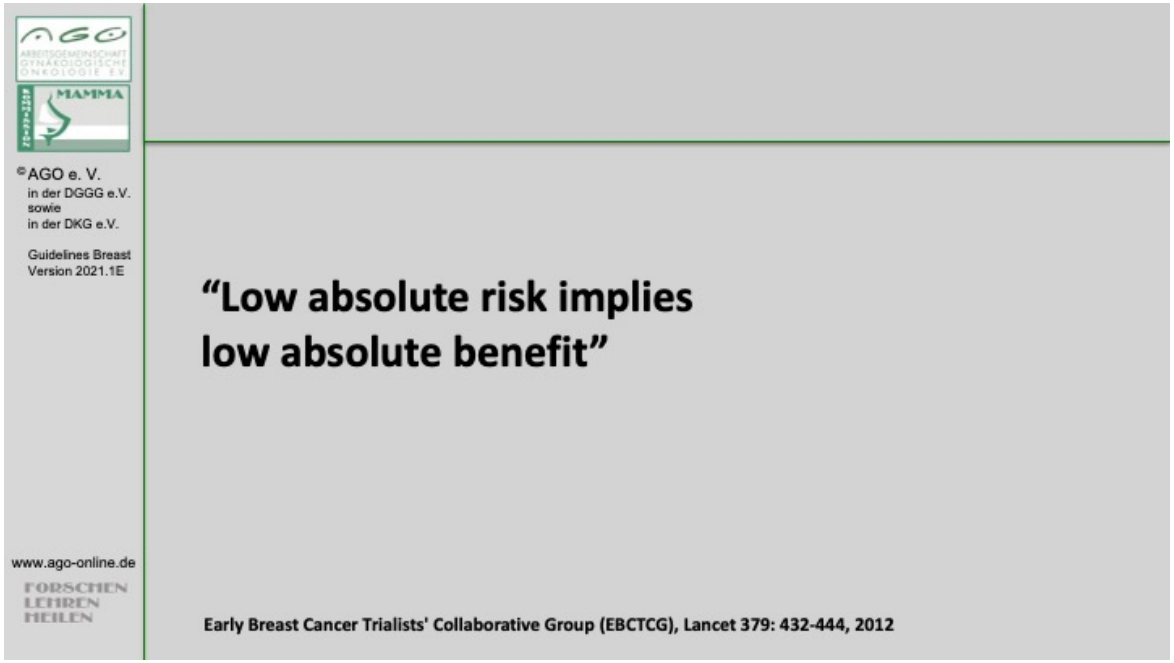

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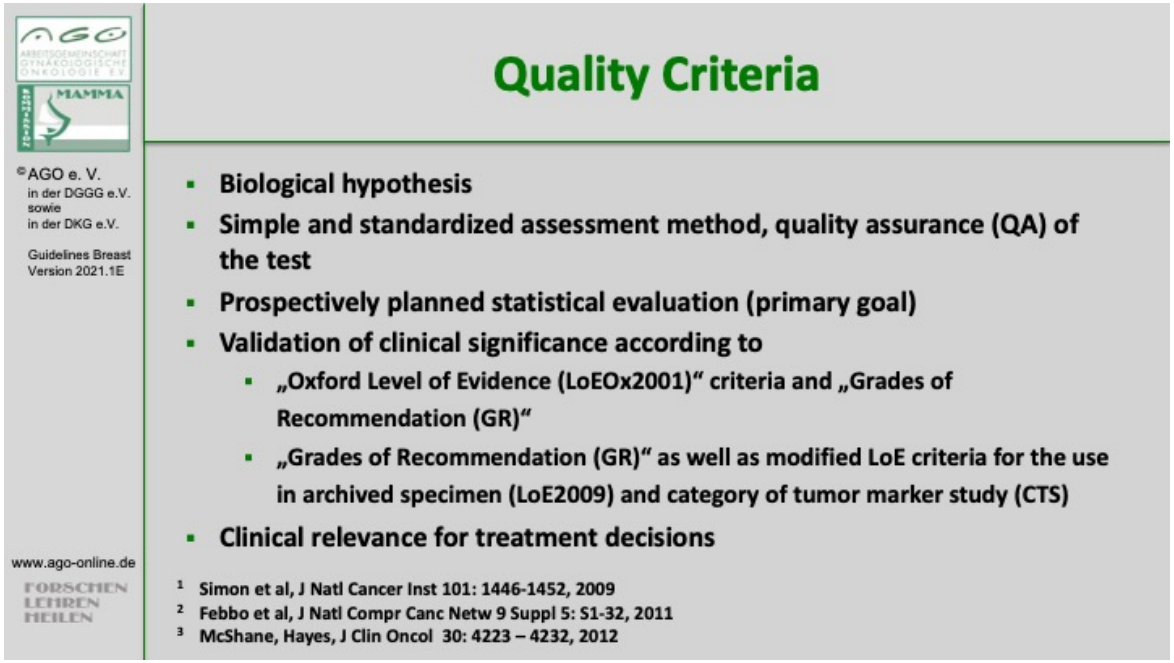

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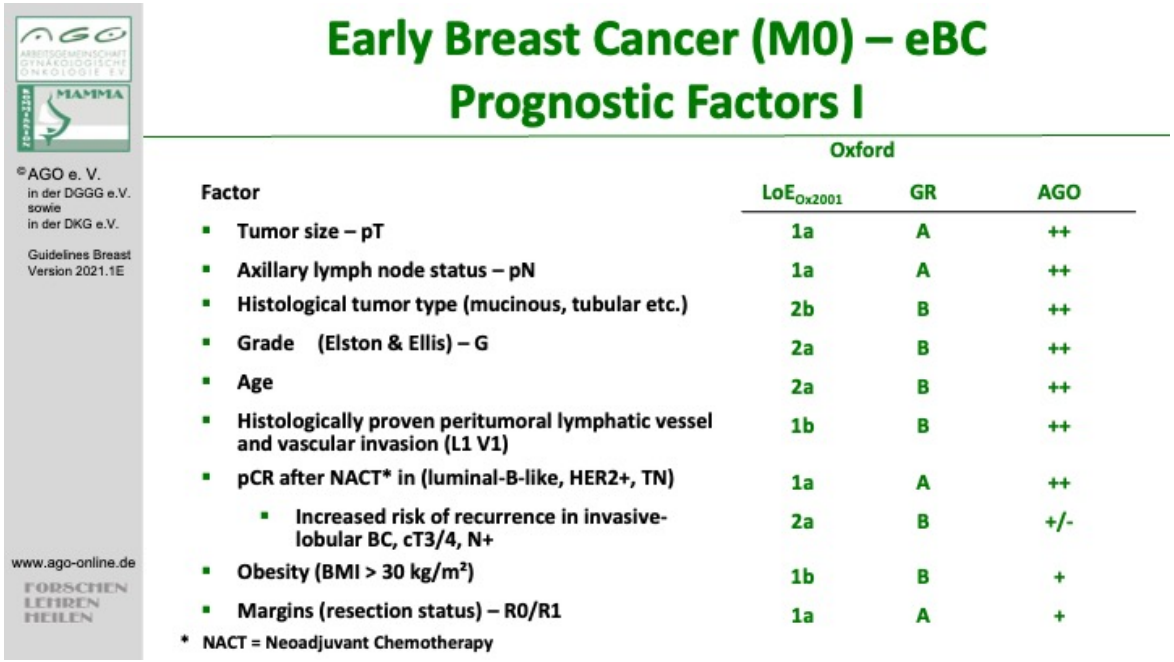

Early Breast Cancer (M0) – eBC
Prognostic Factors I

Factor	Oxford LoE$_{Ox2001}$	Oxford 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/m²)	1b	B	+
▪ Margins (resection status) – R0/R1	1a	A	+

* NACT = Neoadjuvant Chemotherapy

General references

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Tumor size

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Lymph node status

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Histological type (mucinous, tubular etc.)

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Tumor grade (Elston & Ellis)

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Age

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Histologically proven lymph and/or blood vessel invasion

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

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Increased risk of recurrence in invasive-lobular BC, cT3/4, N+

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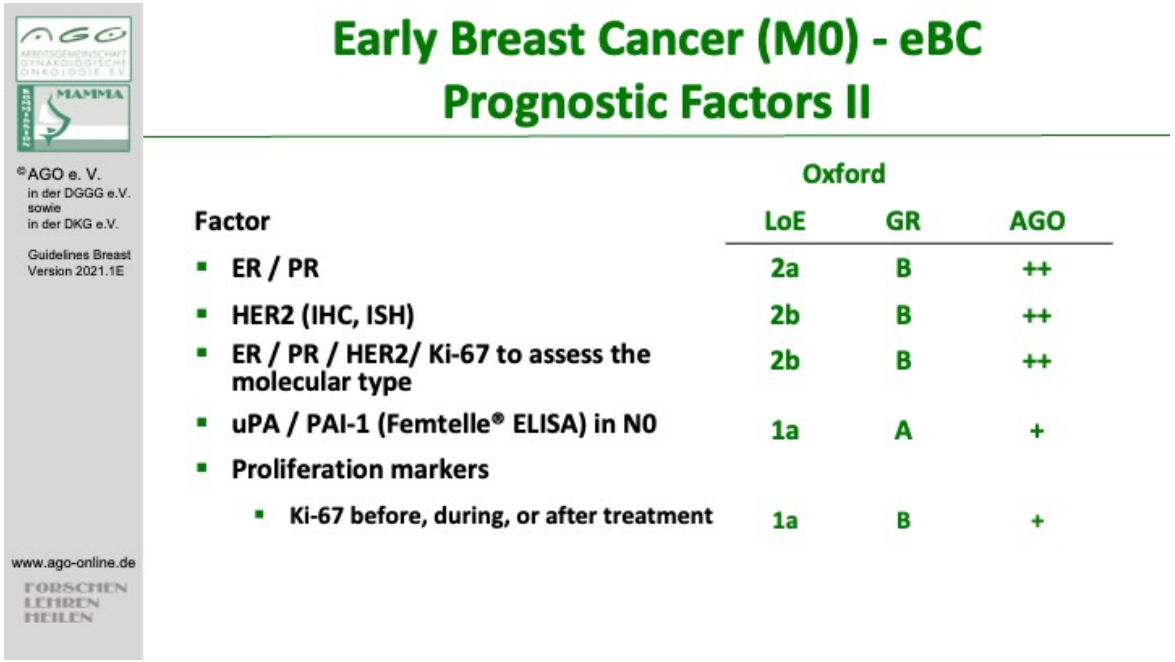

Early Breast Cancer (M0) - eBC
Prognostic Factors II

Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ ER / PR	2a	B	++
▪ HER2 (IHC, ISH)	2b	B	++
▪ ER / PR / HER2/ Ki-67 to assess the molecular type	2b	B	++
▪ uPA / PAI-1 (Femtelle® ELISA) in N0	1a	A	+
▪ Proliferation markers			
▪ Ki-67 before, during, or after treatment	1a	B	+

ER/PR

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uPA/PAI-1

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<u>Ki-67</u>

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<u>Post-treatment Ki-67</u>

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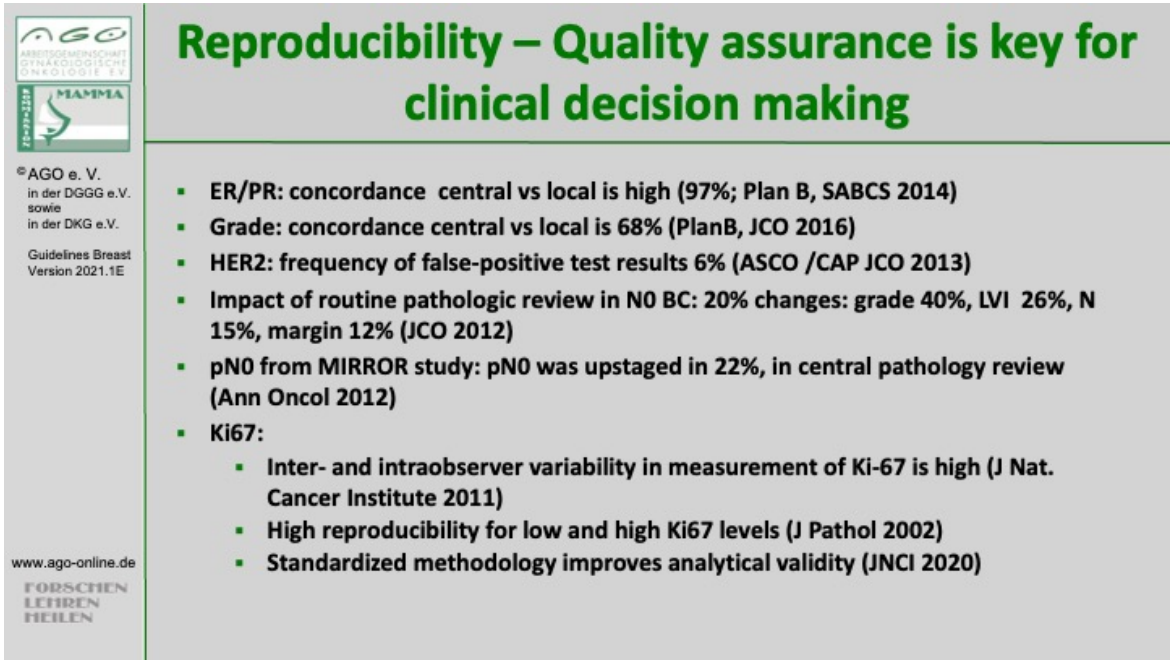

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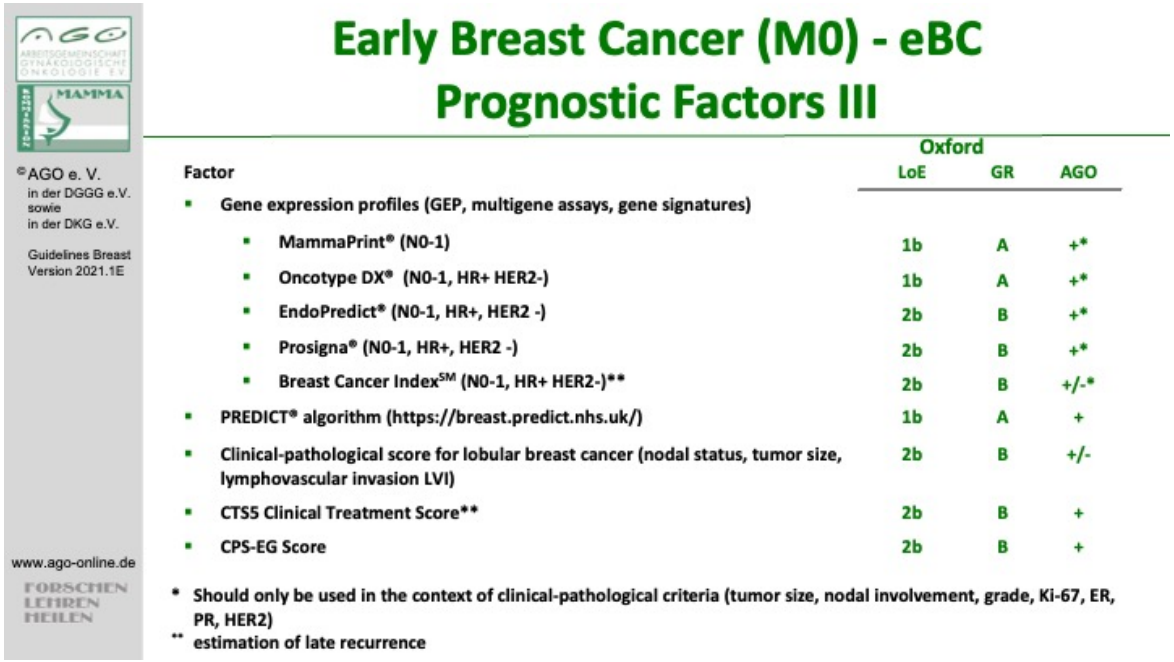

Early Breast Cancer (M0) - eBC
Prognostic Factors III

Factor	Oxford LoE	Oxford GR	Oxford 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	+/-*
▪ 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	+/-
▪ CTS5 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

<u>Gene expression profiles (GEP; Multigene Assays, Gene expression signatures)</u>
(*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)

<u>MammaPrint®</u>

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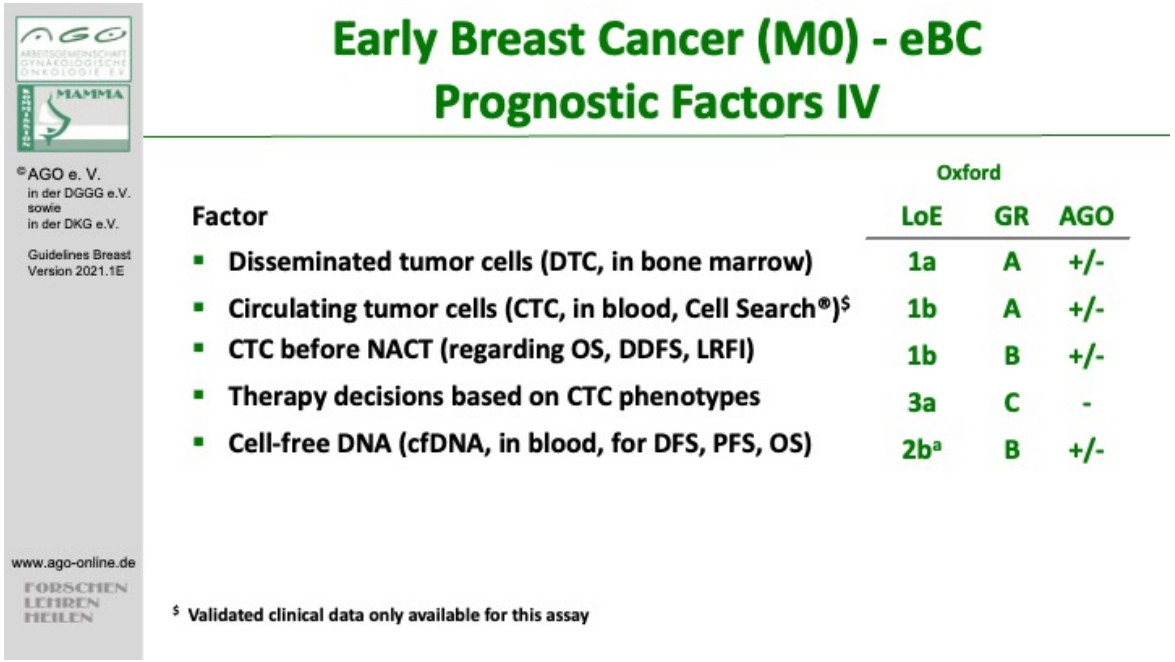

Early Breast Cancer (M0) - eBC
Prognostic Factors IV

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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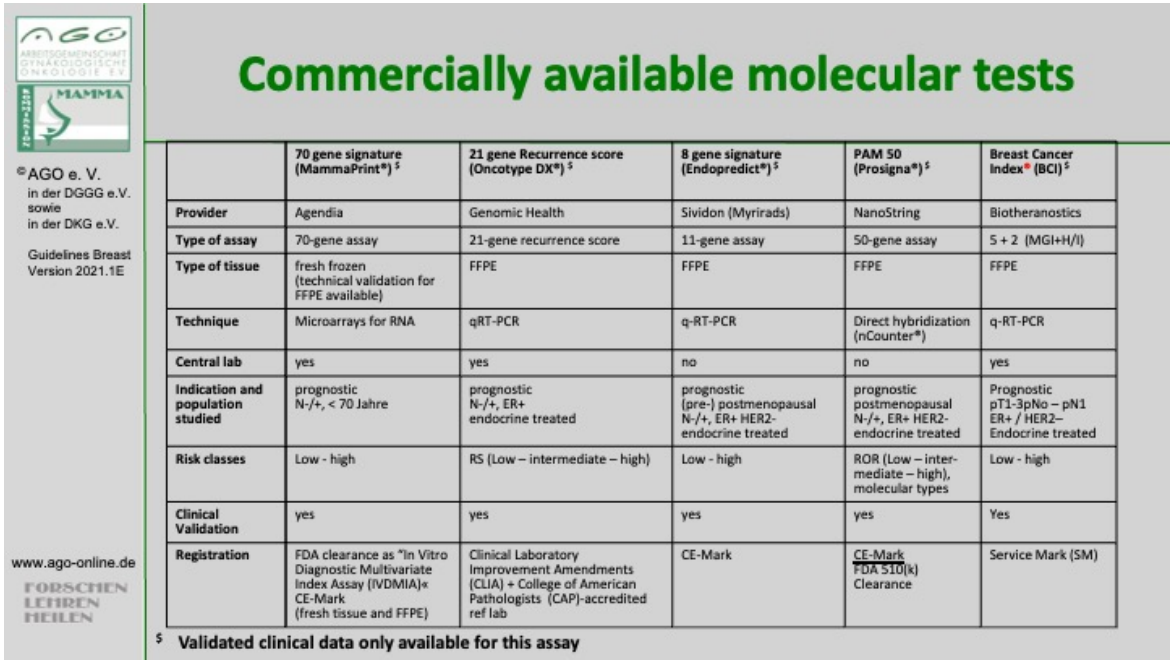

Commercially available molecular tests

	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 (Myrirads)	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 (nCounter®)	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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Prosigna (ROR / PAM50)

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Breast Cancer Index

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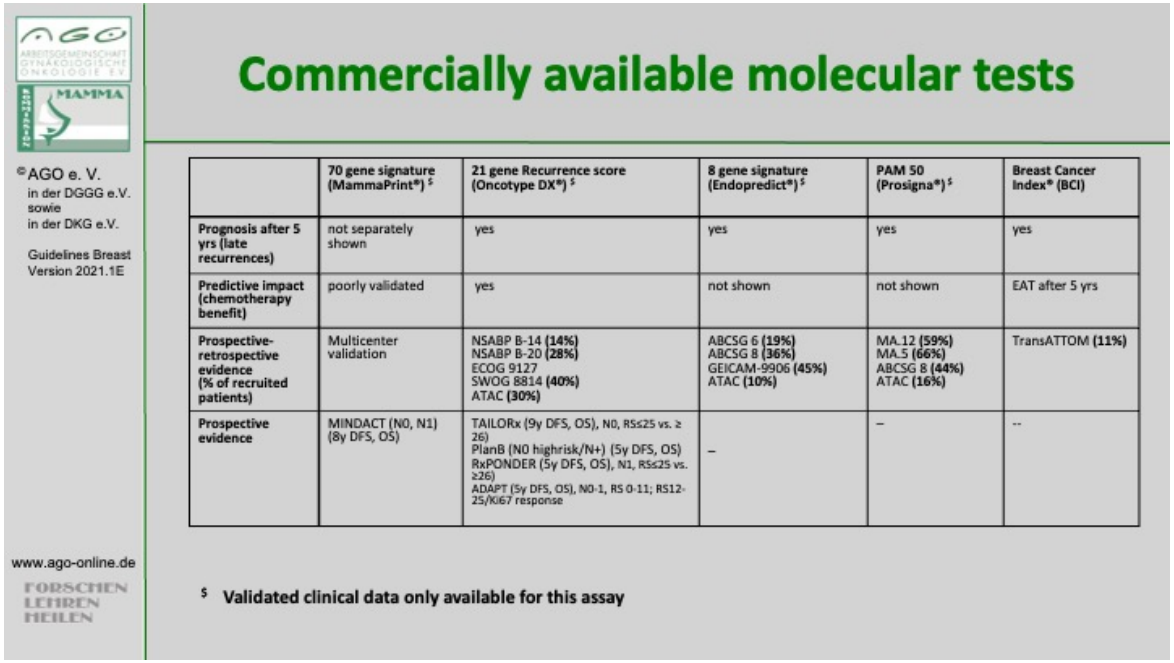

Commercially available molecular tests

	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**

Head to head comparisons

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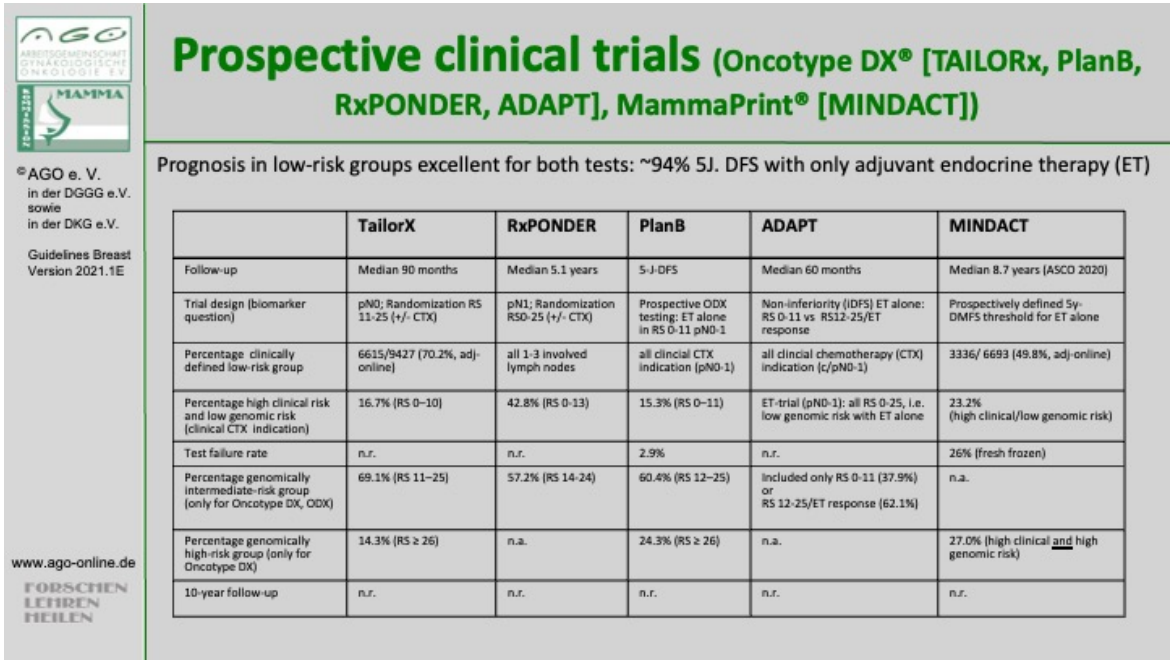

Prospective clinical trials (Oncotype DX® [TAILORx, PlanB, RxPONDER, ADAPT], MammaPrint® [MINDACT])

Prognosis in low-risk groups excellent for both tests: ~94% 5J. 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 clincial CTX indication (pN0-1)	all clincial 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 and high genomic risk)
10-year follow-up	n.r.	n.r.	n.r.	n.r.	n.r.

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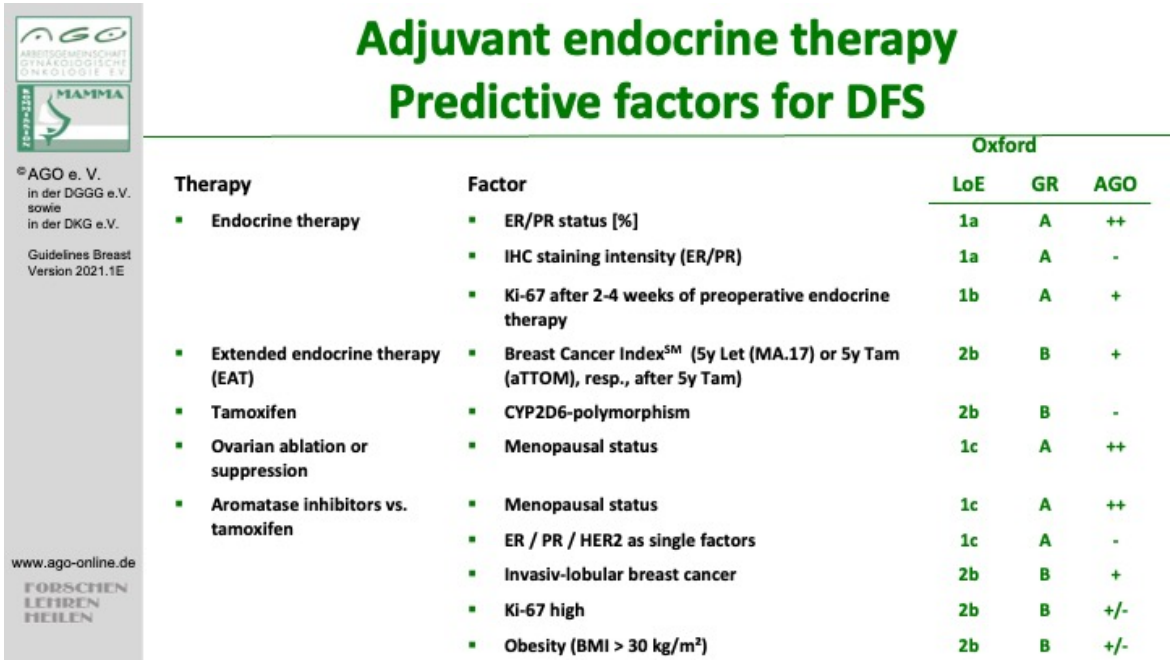

Adjuvant endocrine therapy
Predictive factors for DFS

Therapy	Factor	Oxford LoE	Oxford GR	Oxford AGO
Endocrine therapy	ER/PR status [%]	1a	A	++
	IHC staining intensity (ER/PR)	1a	A	-
	Ki-67 after 2-4 weeks of preoperative endocrine therapy	1b	A	+
Extended endocrine therapy (EAT)	Breast Cancer Index^{SM} (5y Let (MA.17) or 5y Tam (aTTOM), resp., after 5y 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/m²)	2b	B	+/-

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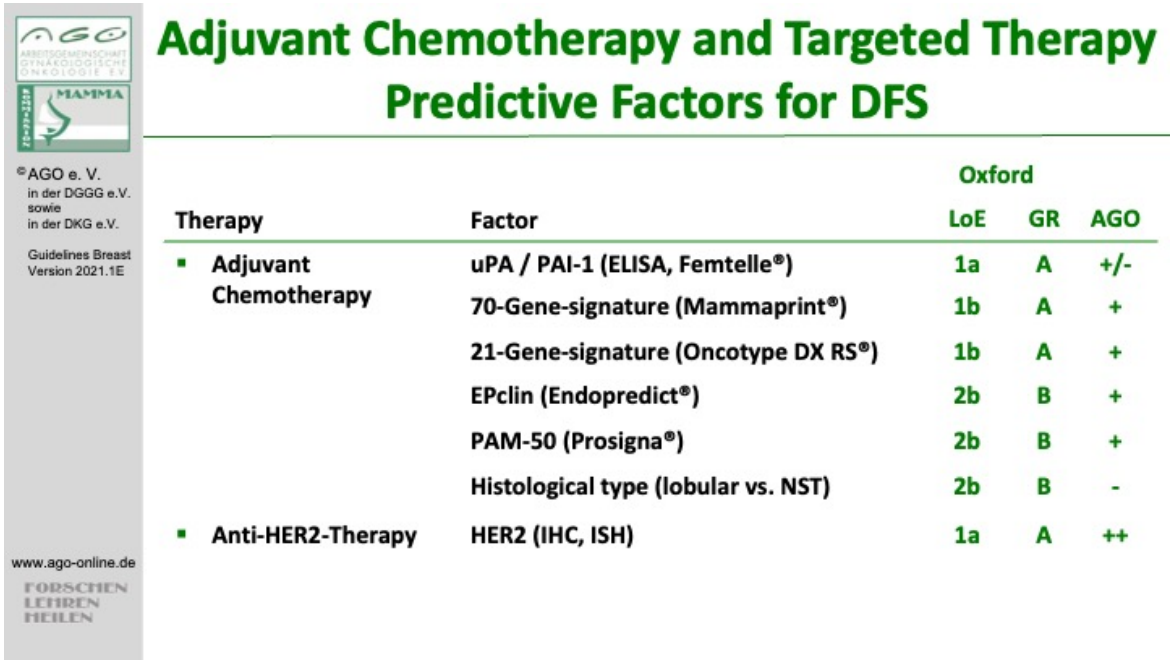

Adjuvant Chemotherapy and Targeted Therapy
Predictive Factors for DFS

Therapy	Factor	Oxford LoE	Oxford GR	Oxford 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	-
▪ Anti-HER2-Therapy	HER2 (IHC, ISH)	1a	A	++

uPA/PAI-1

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EPclin (EndoPredict®)

1. Sestak I, Martín M, Dubsky P et al. Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone. Breast Cancer Res Treat. 2019 Jul;176(2):377-386.

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1. De Nonneville A, Jauffret C, Goncalves A. Adjuvant chemotherapy in lobular carcinoma of the breast: a clinicopathological score identifies high-risk patient with survival benefit Breast Cancer Res Treat. 2019 Jun;175(2):379-387.
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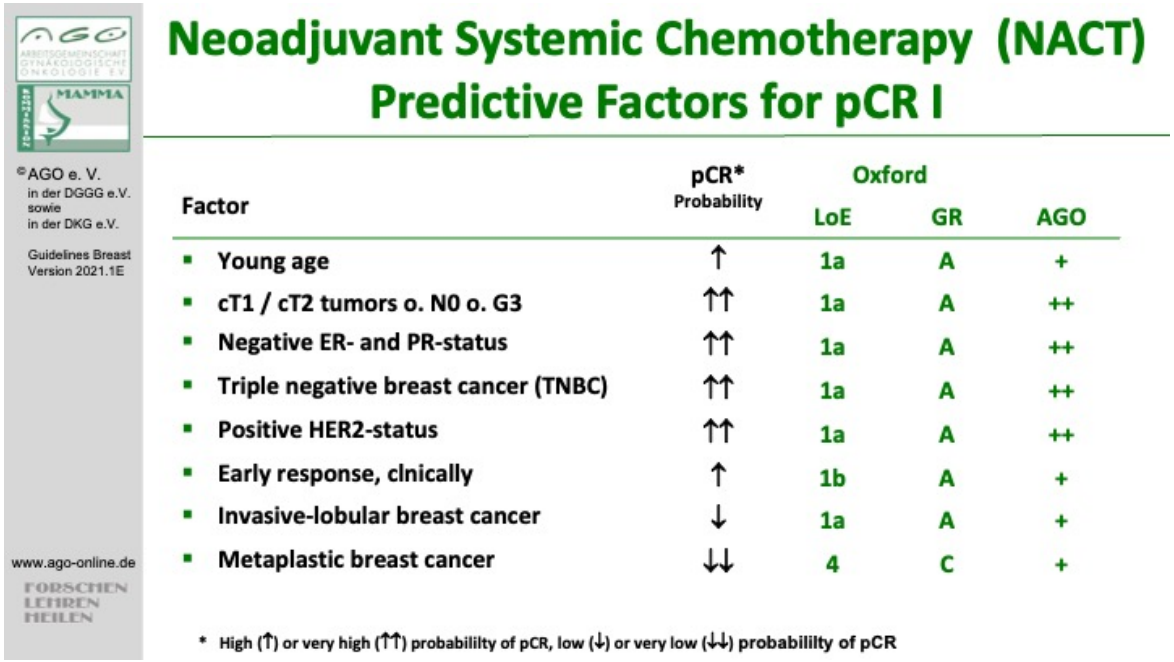
Anti-HER2 therapy

see evidence in chapter "Chemotherapy and targeted therapy"



Neoadjuvant Systemic Chemotherapy (NACT)
Predictive Factors for pCR I

Factor	pCR* Probability	Oxford LoE	Oxford GR	Oxford AGO
▪ Young age	↑	1a	A	+
▪ cT1 / cT2 tumors o. N0 o. G3	↑↑	1a	A	++
▪ Negative ER- and PR-status	↑↑	1a	A	++
▪ Triple negative breast cancer (TNBC)	↑↑	1a	A	++
▪ Positive HER2-status	↑↑	1a	A	++
▪ Early response, clnically	↑	1b	A	+
▪ Invasive-lobular breast cancer	↓	1a	A	+
▪ Metaplastic breast cancer	↓↓	4	C	+

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

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Metaplastic breast cancer

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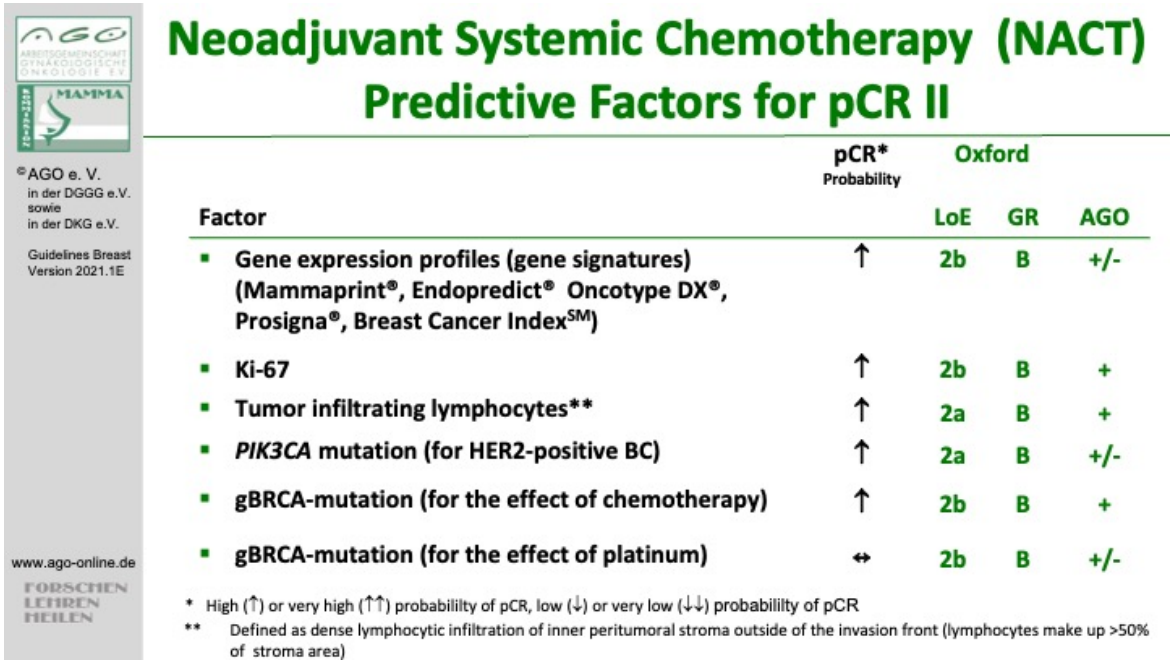

Neoadjuvant Systemic Chemotherapy (NACT)
Predictive Factors for pCR II

Factor	pCR* Probability	Oxford LoE	Oxford GR	Oxford 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 (↑↑) probabililty of pCR, low (↓) or very low (↓↓) probabililty of pCR

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

TIL

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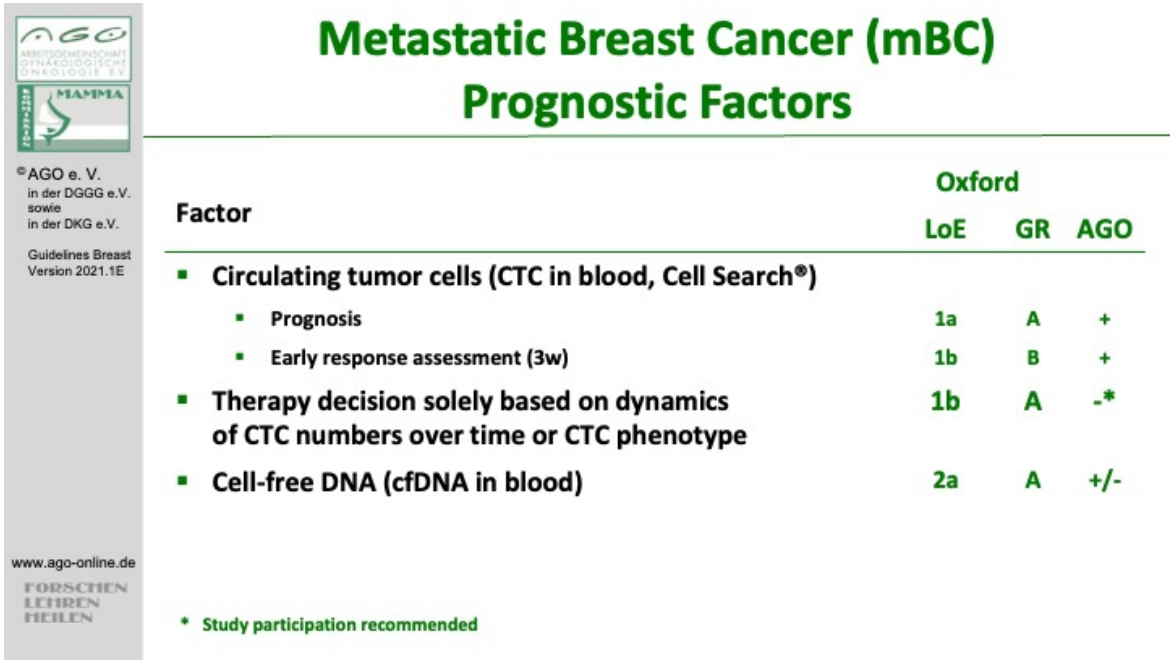

Metastatic Breast Cancer (mBC)
Prognostic Factors

Factor	Oxford LoE	GR	AGO
▪ Circulating tumor cells (CTC in blood, Cell Search®)			
▪ Prognosis	1a	A	+
▪ Early response assessment (3w)	1b	B	+
▪ Therapy decision solely based on dynamics of CTC numbers over time or CTC phenotype	1b	A	-*
▪ Cell-free DNA (cfDNA in blood)	2a	A	+/-

* Study participation recommended

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CTC

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Guidelines Breast
Version 2021.1E

Treatment of Metastatic Breast Cancer
Predictive Factors for response

Therapy	Factor	Oxford LoE	Oxford 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 (IC) (primary tumor or metastasis)	1a	B	+
▪ PARP-Inhibitors	gBRCA1/2-mutation	1a	A	++
▪ Bone-modifying drugs	Bone metastasis	1a	A	++
▪ Any therapy	CTC monitoring	1b	A	+*

* In clinical trials: # see chapter „pathology"

Endocrine therapy

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Endocrine therapy - ESR1

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2. Fribbens C, Garcia Murillas I, Beaney M et al. (2018) Tracking evolution of aromatase inhibitor resistance with circulating tumour DNA analysis in metastatic breast cancer. Ann Oncol.29:145-153. doi: 10.1093/annonc/mdx483
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Alpelisib

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Chemotherapy

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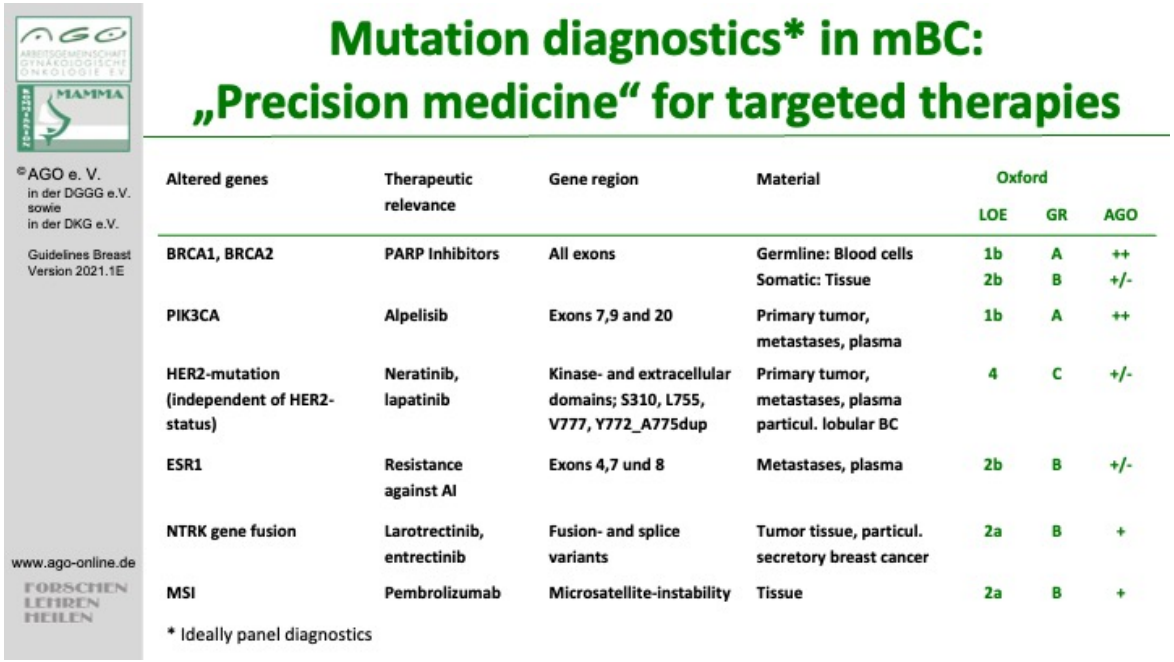

Mutation diagnostics* in mBC: „Precision medicine“ for targeted therapies

Altered genes	Therapeutic relevance	Gene region	Material	Oxford LOE	Oxford GR	Oxford AGO
BRCA1, BRCA2	PARP Inhibitors	All exons	Germline: Blood cells Somatic: Tissue	1b 2b	A B	++ +/-
PIK3CA	Alpelisib	Exons 7,9 and 20	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 und 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

BRCA1/2:

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2. Kaufman B, Shapira-Frommer R, Schmutzler RK et al. (2015) Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015 Jan 20;33(3):244-50. doi: 10.1200/JCO.2014.56.2728.

PIK3CA:

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Negative, Hormone Receptor-Positive Advanced Breast Cancer. Clin Cancer Res. 2018 Sep 15;24(18):4380-4387.

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4. Xu X, De Angelis C, Burke KA, et al. HER2 Reactivation through Acquisition of the HER2 L755S Mutation as a Mechanism of Acquired Resistance to HER2-targeted Therapy in HER2(+) Breast Cancer. Clin Cancer Res 2017;23: 5123-34.

ESR1:

1. Dustin D, Gu G, Fuqua SAW (2019) ESR1 mutations in breast cancer. Cancer 125:3714-3728 doi: 10.1002/cncr.32345.
2. Fribbens C, Garcia Murillas I, Beaney M et al. (2018) Tracking evolution of aromatase inhibitor resistance with circulating tumour DNA analysis in metastatic breast cancer. Ann Oncol.29:145-153. doi: 10.1093/annonc/mdx483
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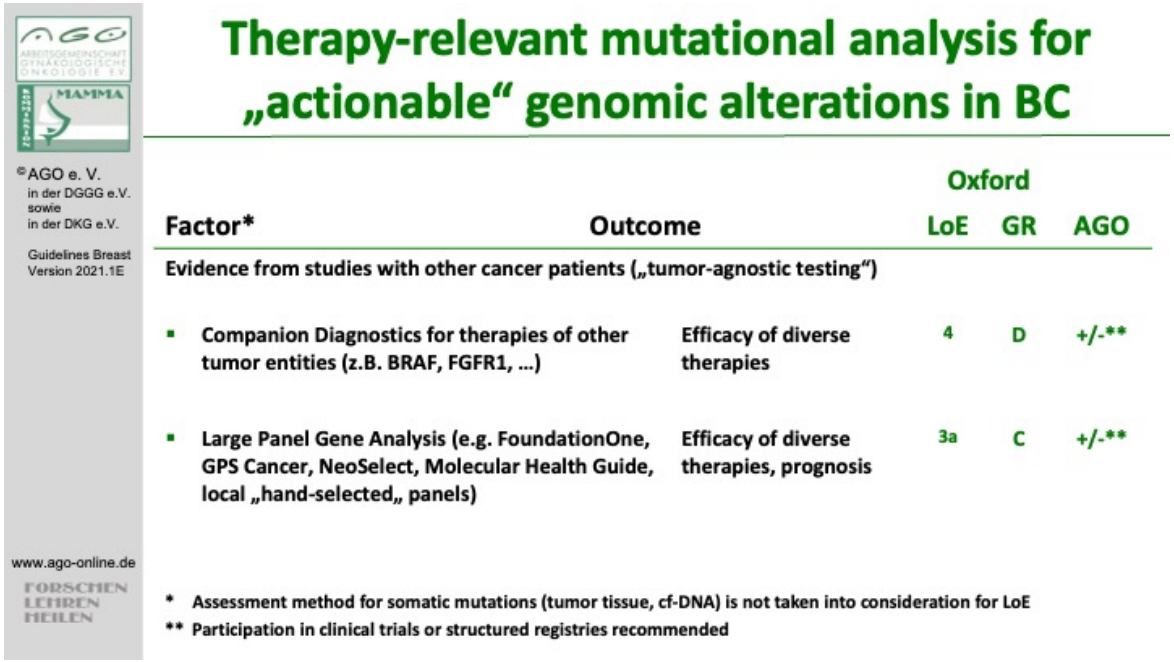
NTRK:

1. Cocco E, Scaltriti M, Drilon A (2018) NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol. 15(:731-747. doi: 10.1038/s41571-018-0113-0.

MSI:

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



Therapy-relevant mutational analysis for „actionable“ genomic alterations in BC

Factor*	Outcome	Oxford LoE	Oxford GR	AGO
Evidence from studies with other cancer patients („tumor-agnostic testing“)				
▪ Companion Diagnostics for therapies of other tumor entities (z.B. 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	+/-**

* Assessment method for somatic mutations (tumor tissue, cf-DNA) is not taken into consideration for LoE

** Participation in clinical trials or structured registries recommended

NGS in breast cancer:

1. Mosele F, Remon J, Mateo J, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. Ann Oncol. 2020 Nov;31(11):1491-1505.
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