Guidelines Breast
Version 2019.1D

Prognostische und prädiktive Faktoren

Data bases screened

Pubmed 2008 - 2018, ASCO 2003 – 2018, SABCS 2003 – 2018, Cochrane data base (n.d.)

Guidelines screened

1. Curigliano G, Burstein HJ, P Winer E, et al. Panel Members of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2017. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. Ann Oncol. 2019 Jan 9. doi: 10.1093/annonc/mdy537. [Epub ahead of print]
2. ABC3: Cardoso F, Costa A, Senkus E et al. 3rd ESO-ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3). Breast. 2017 Feb;31:244-259.
3. NCCN 2016: www.nccn.org
4. ASCO 2016: 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.

1. Clark GM et al. Prognostic and predictive factors. In: Diseases of the breast, 2nd edition: Seiten 489-514. Harris JR, Lippmann ME, Morrow M, Osborne CK (Hrsg). Lippincott-Raven Publishers, Philadelphia 2000.
2. Harbeck N, Gnant M. Breast cancer. Lancet. 2016 Nov 16. pii: S0140-6736(16)31891-8.

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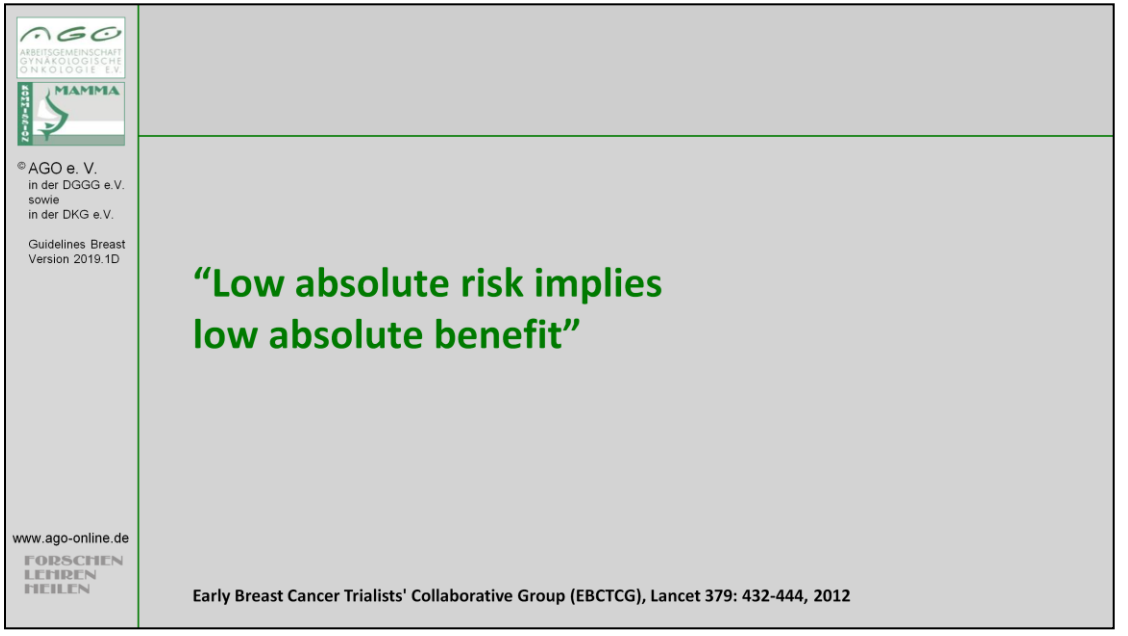
Definition

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.**



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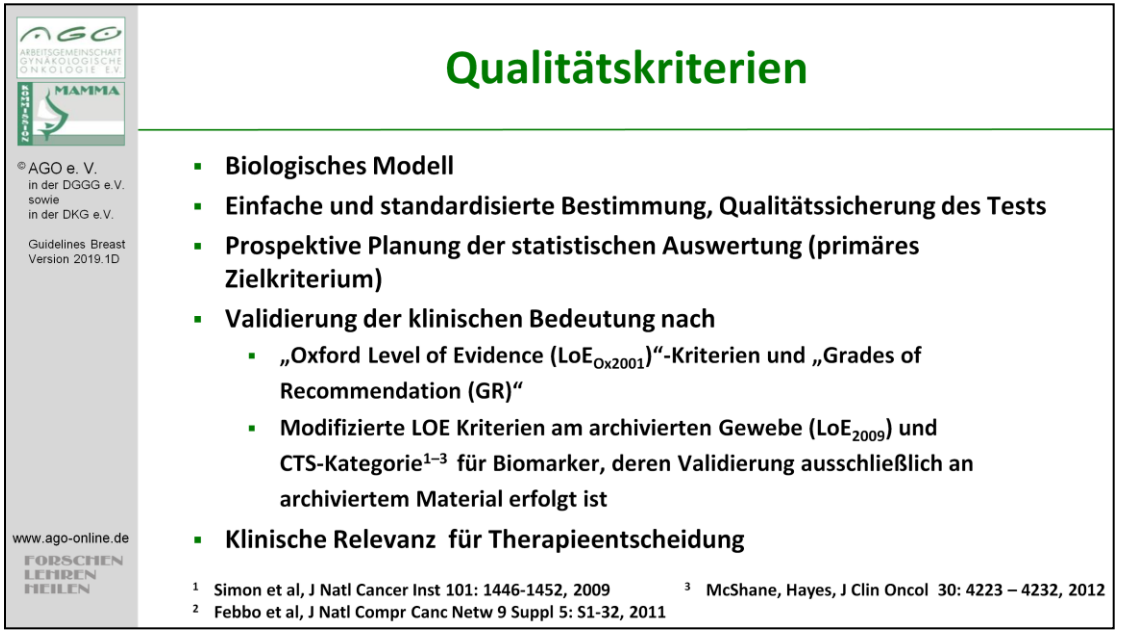
2. Nielsen T, Jensen B, et al High risk premenopausal luminal A breast cancer patients derive no benefit from adjuvant chemotherapy: results from DBCG77B, SABCS 2015S1-08



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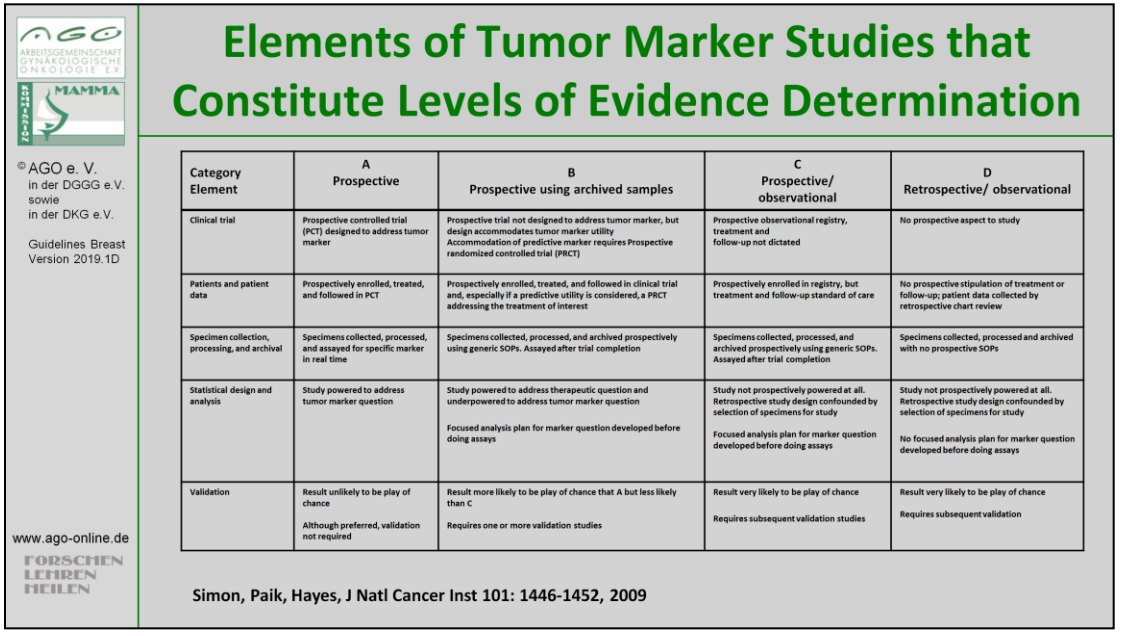

Elements of Tumor Marker Studies that Constitute Levels of Evidence Determination

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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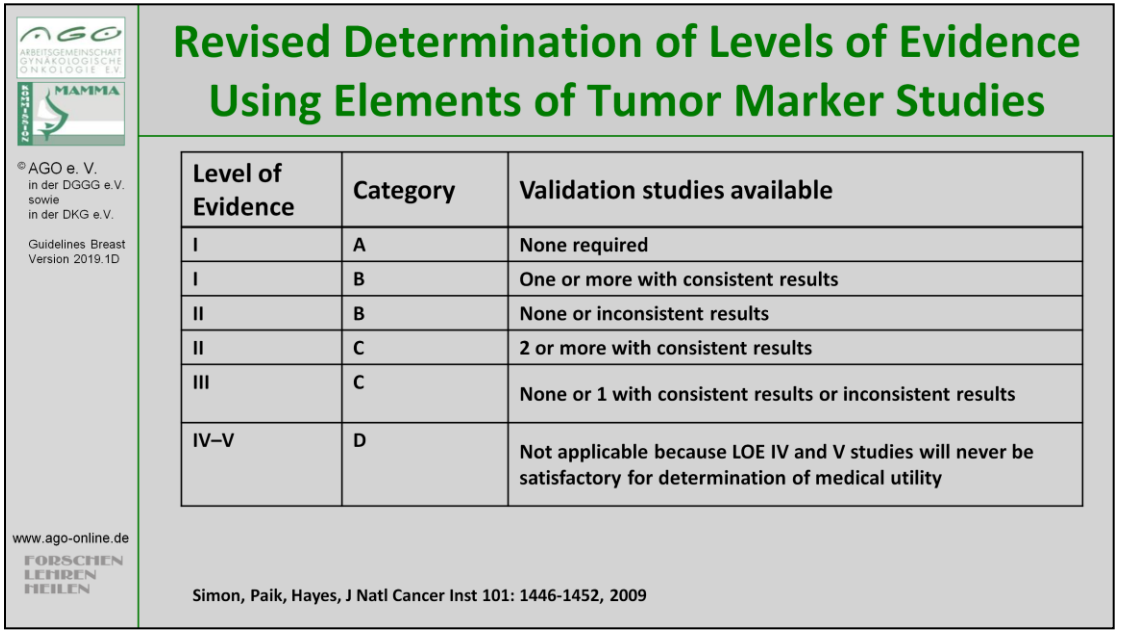

Revised Determination of Levels of Evidence Using Elements of Tumor Marker Studies

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

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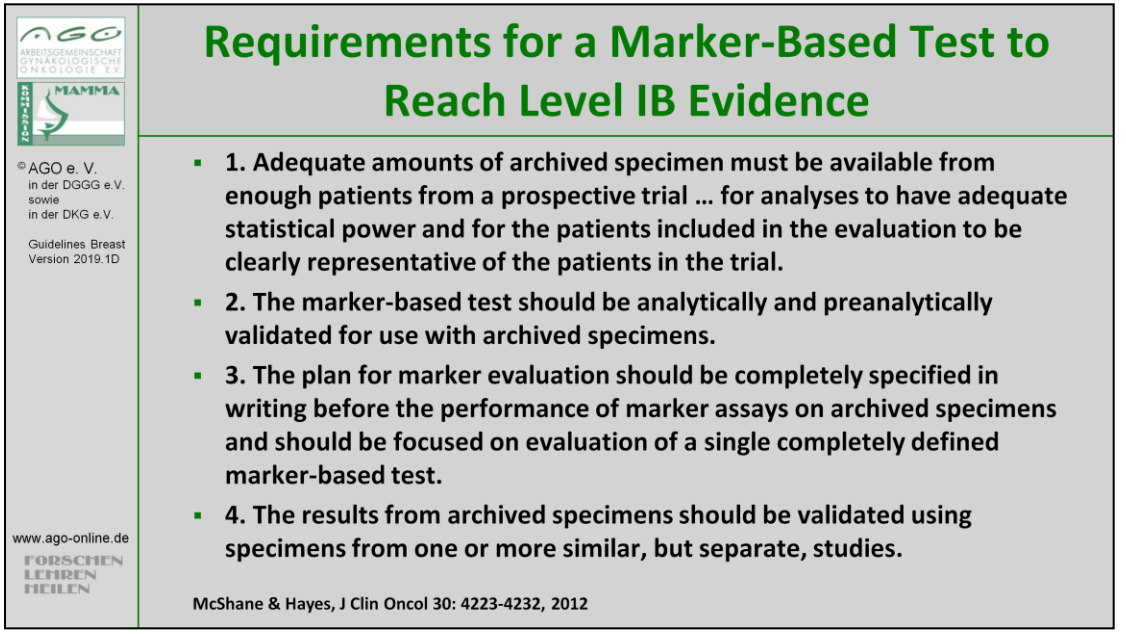

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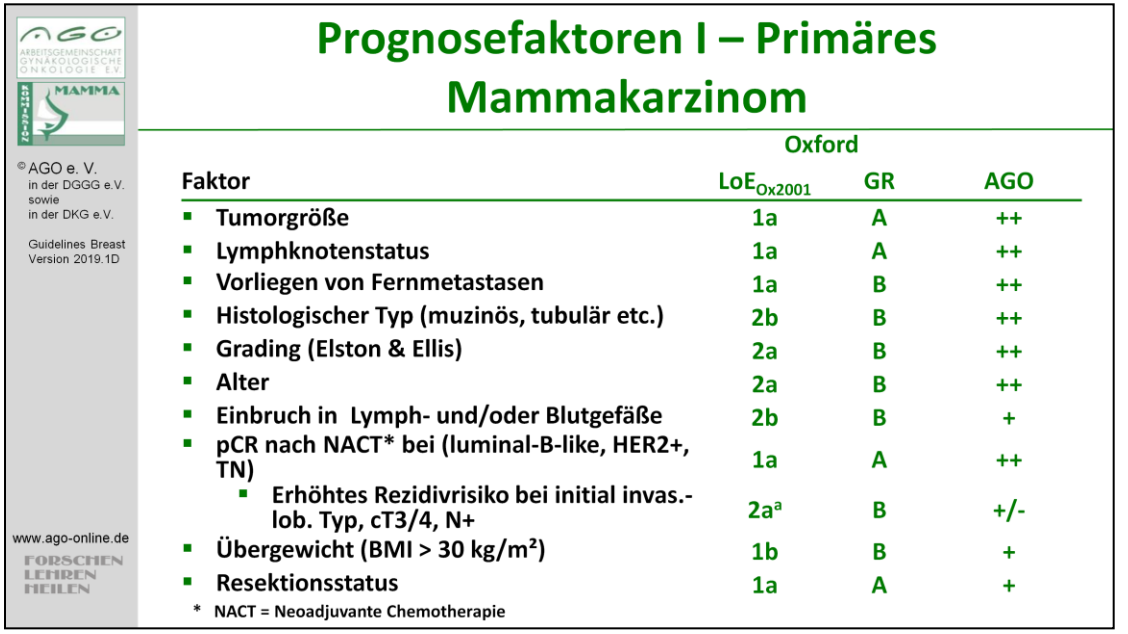

1. Harris LN, Ismaila N, McShane LM et al.: Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2016 Apr 1;34(10):1134-50.
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3. Houssami, N., et al., The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol, 2014. 21(3): p. 717-30.

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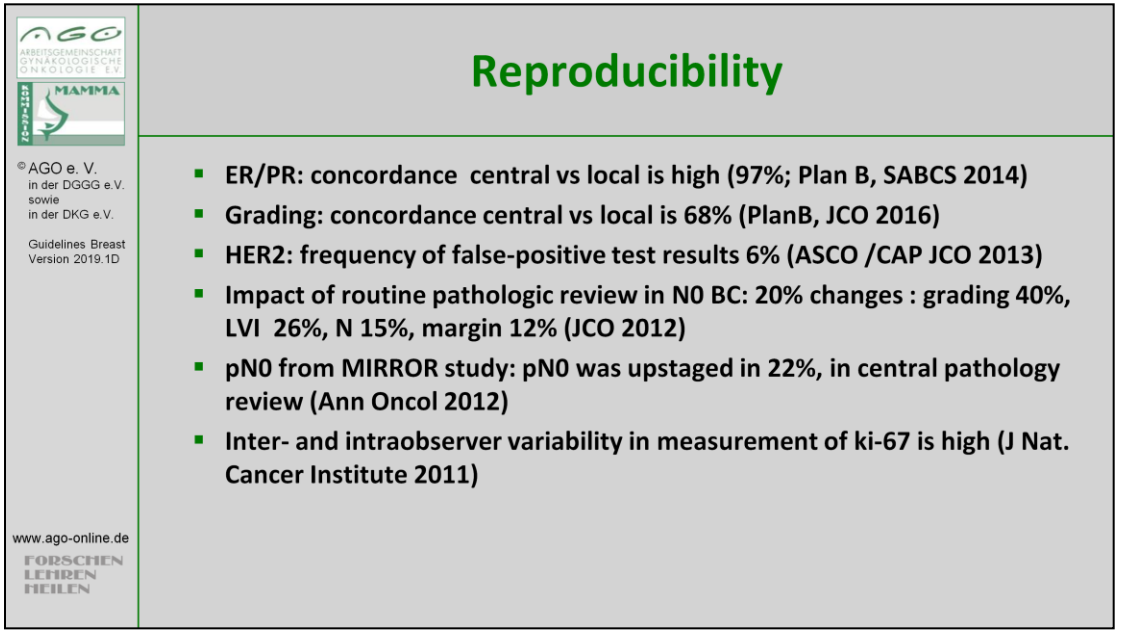

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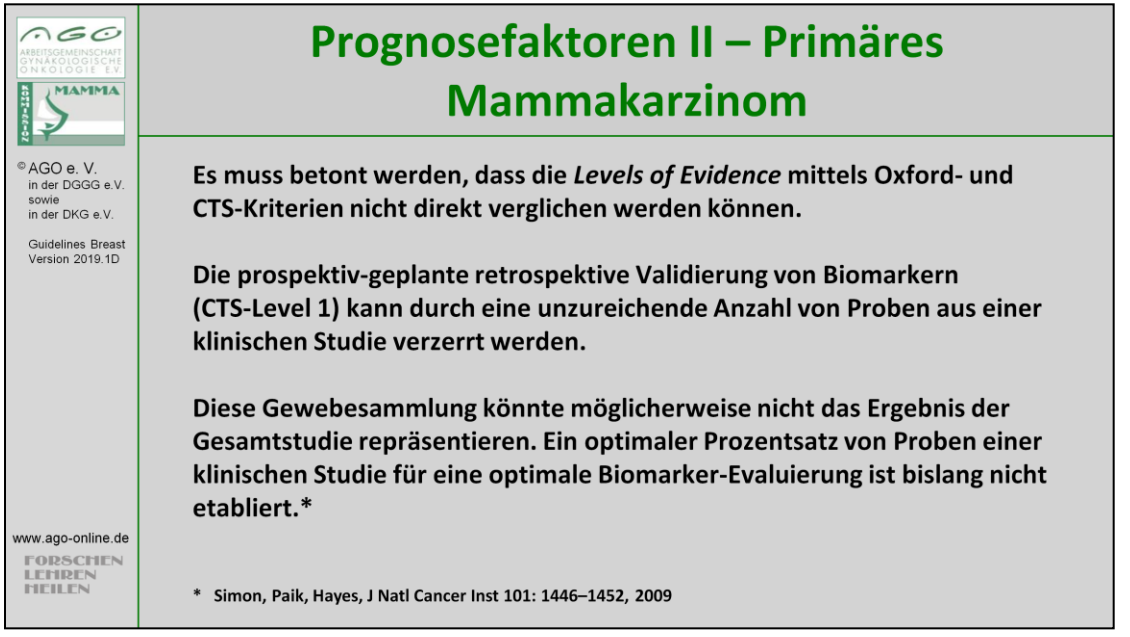

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HER2

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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.
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Post-treatment Ki-67

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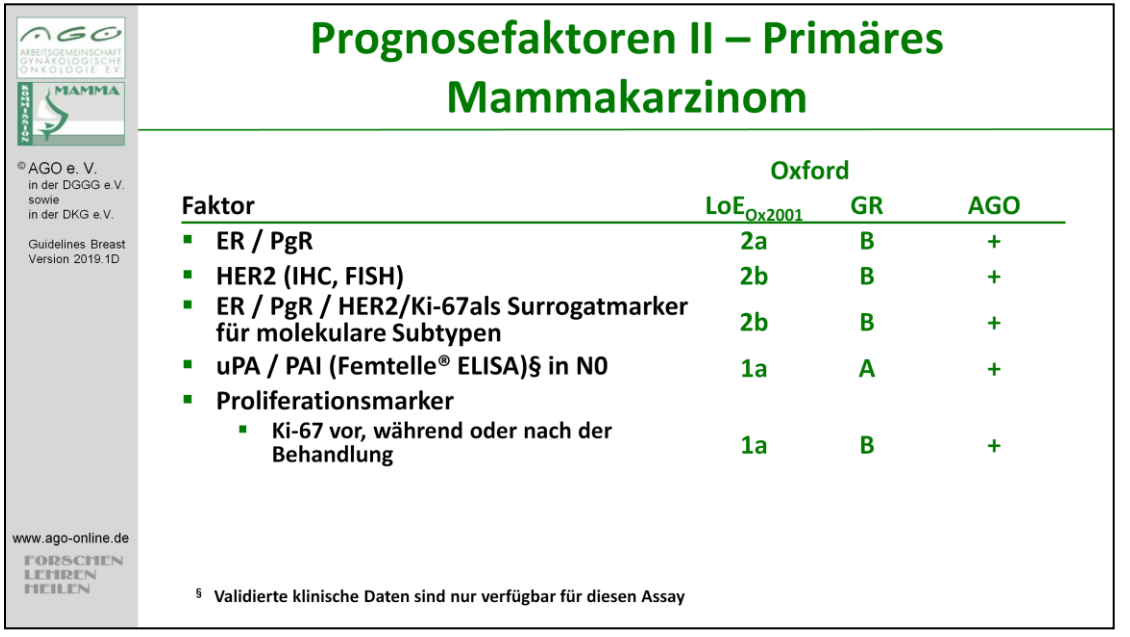

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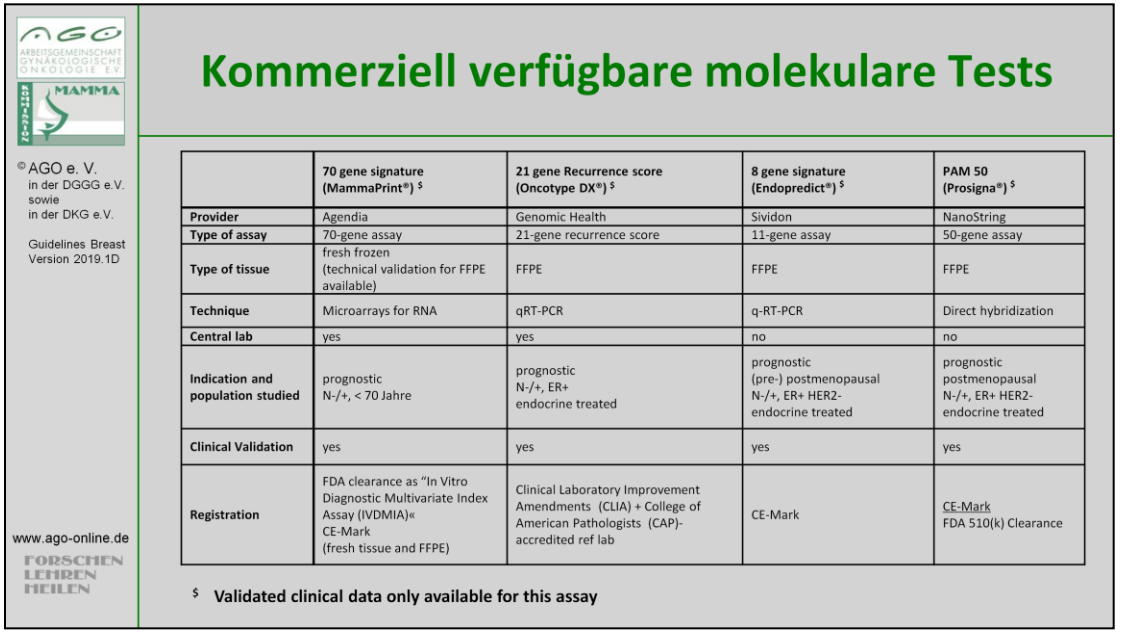

Endopredict

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Mammaprint

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2. Drukker CA, Elias SG, Nijenhuis MV, et al. Gene expression profiling to predict the risk of locoregional recurrence in breast cancer: a pooled analysis. Breast Cancer Res Treat. 2014 Dec;148(3):599-613.
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Oncotype

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11. Geyer CE Jr, Tang G, Mamounas EP, et al. 21-Gene assay as predictor of chemotherapy benefit in HER2-negative breast cancer. NPJ Breast Cancer. 2018 Nov 14;4:37.
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Prosigna (ROR / PAM50)

1. Chia, S.K., Bramwell, V.H., Tu, Det al. 2012. A 50-gene intrinsic subtype classifier for prognosis and prediction of benefit from adjuvant tamoxifen. Clin. Cancer Res. 18, 4465–4472.
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Multiple assays

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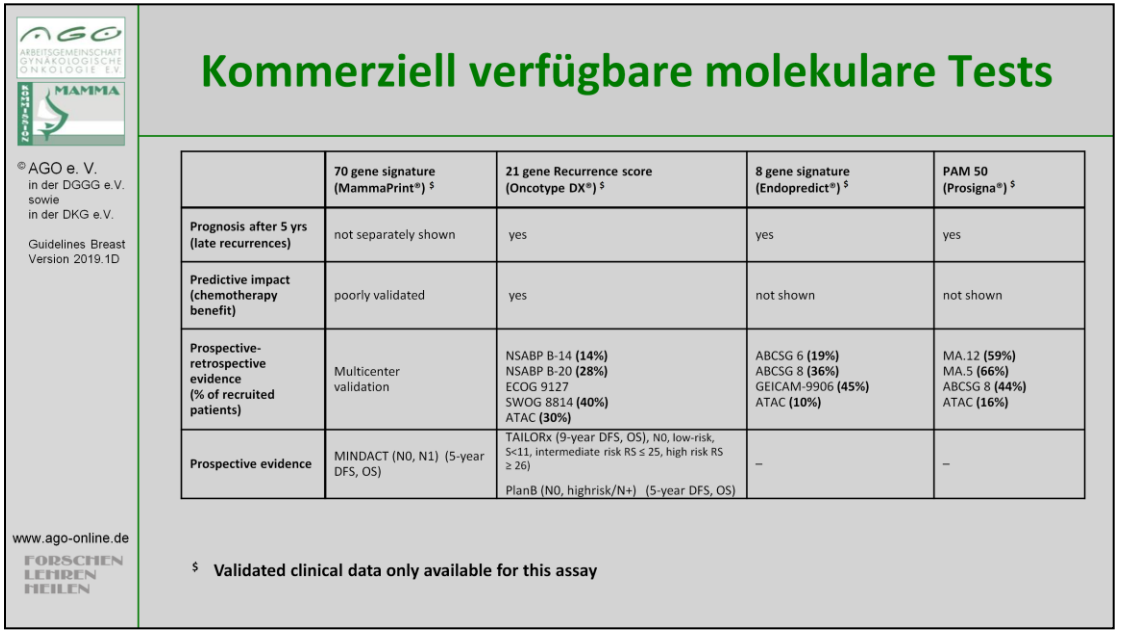

Kommerziell verfügbare molekulare Tests

	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**

Endopredict

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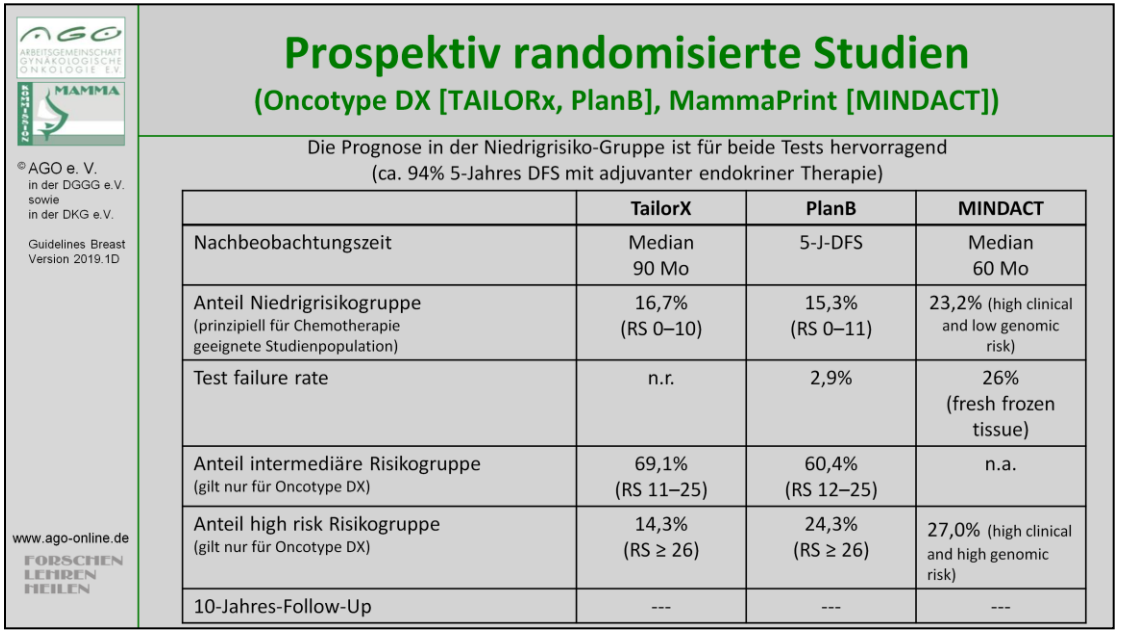

Prospektiv randomisierte Studien

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

Guidelines Breast
Version 2019.1D

Die Prognose in der Niedrigrisiko-Gruppe ist für beide Tests hervorragend
(ca. 94% 5-Jahres DFS mit adjuvanter endokriner Therapie)

	TailorX	PlanB	MINDACT
Nachbeobachtungszeit	Median 90 Mo	5-J-DFS	Median 60 Mo
Anteil Niedrigrisikogruppe (prinzipiell für Chemotherapie geeignete Studienpopulation)	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)
Anteil intermediäre Risikogruppe (gilt nur für Oncotype DX)	69,1% (RS 11–25)	60,4% (RS 12–25)	n.a.
Anteil high risk Risikogruppe (gilt nur für Oncotype DX)	14,3% (RS ≥ 26)	24,3% (RS ≥ 26)	27,0% (high clinical and high genomic risk)
10-Jahres-Follow-Up	---	---	---

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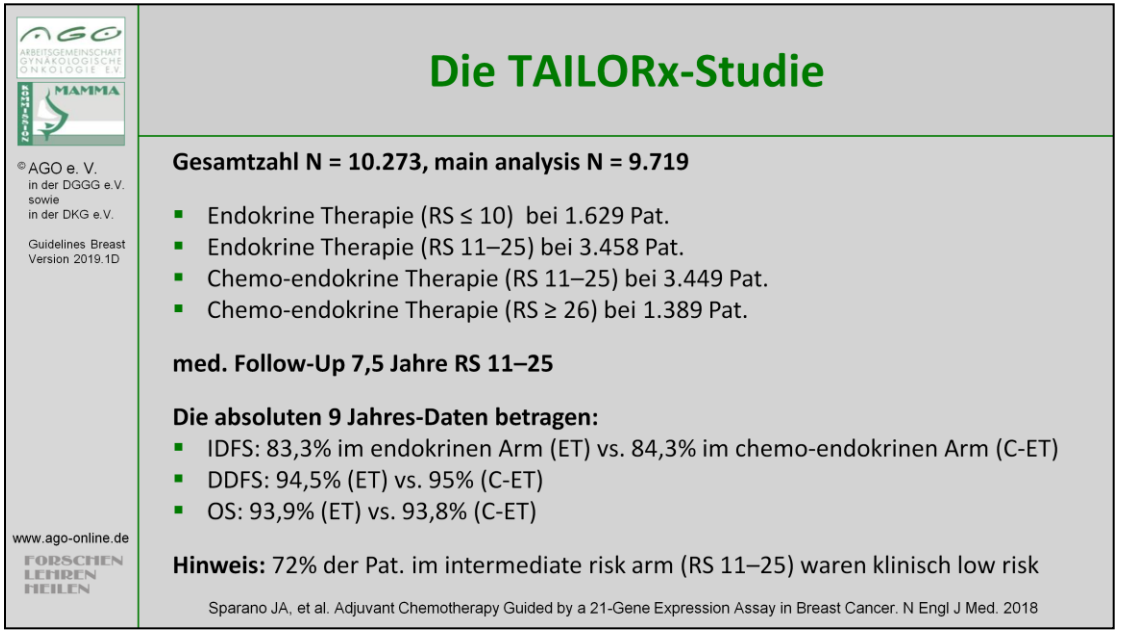
3. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2018 Jul 12;379(2):111-121.

Several tests

1. Bartlett JM, Bayani J, Marshall A, et al; OPTIMA TMG. Comparing Breast Cancer Multiparameter Tests in the OPTIMA Prelim Trial: No Test Is More Equal Than the Others. J Natl Cancer Inst. 2016 Apr 29;108(9).



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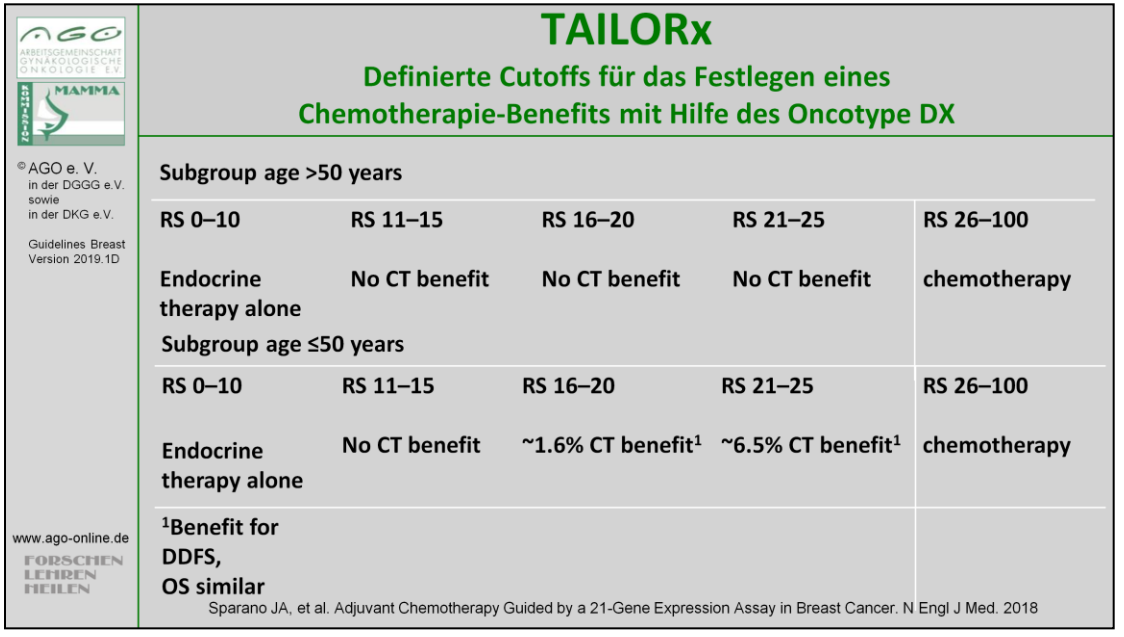

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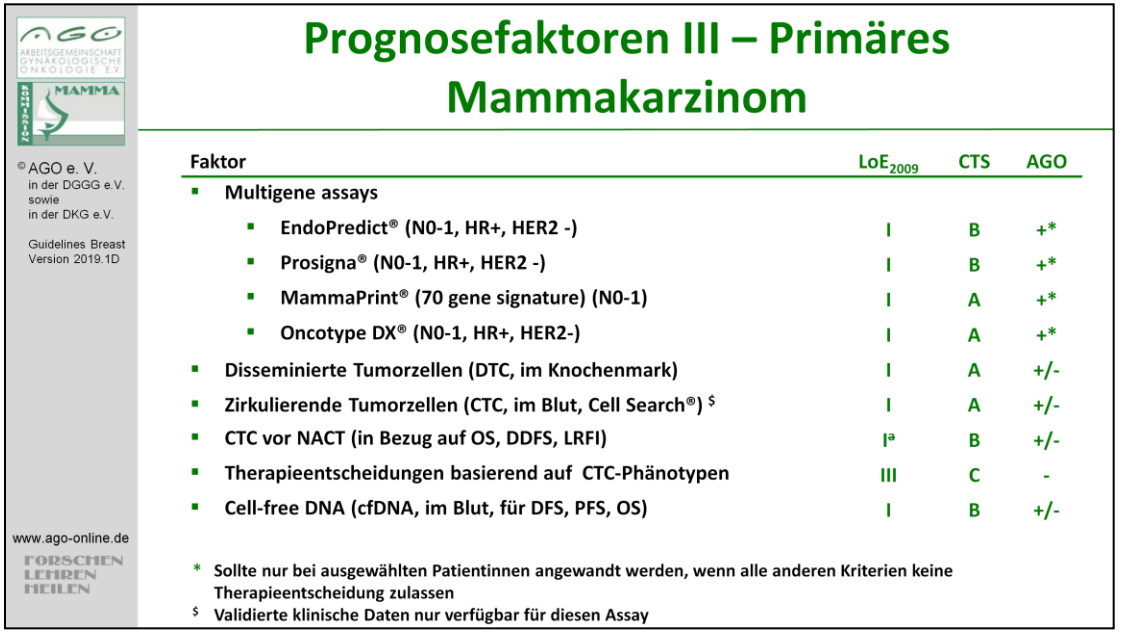

Prognosefaktoren III – Primäres Mammakarzinom

Faktor	LoE_{2009}	CTS	AGO
▪ Multigene assays			
▪ EndoPredict® (N0-1, HR+, HER2 -)	I	B	+*
▪ Prosigna® (N0-1, HR+, HER2 -)	I	B	+*
▪ MammaPrint® (70 gene signature) (N0-1)	I	A	+*
▪ Oncotype DX® (N0-1, HR+, HER2-)	I	A	+*
▪ Disseminierte Tumorzellen (DTC, im Knochenmark)	I	A	+/-
▪ Zirkulierende Tumorzellen (CTC, im Blut, Cell Search®) $	I	A	+/-
▪ CTC vor NACT (in Bezug auf OS, DDFS, LRFI)	I^a	B	+/-
▪ Therapieentscheidungen basierend auf CTC-Phänotypen	III	C	-
▪ Cell-free DNA (cfDNA, im Blut, für DFS, PFS, OS)	I	B	+/-

* Sollte nur bei ausgewählten Patientinnen angewandt werden, wenn alle anderen Kriterien keine Therapieentscheidung zulassen

$ Validierte klinische Daten nur verfügbar für diesen Assay

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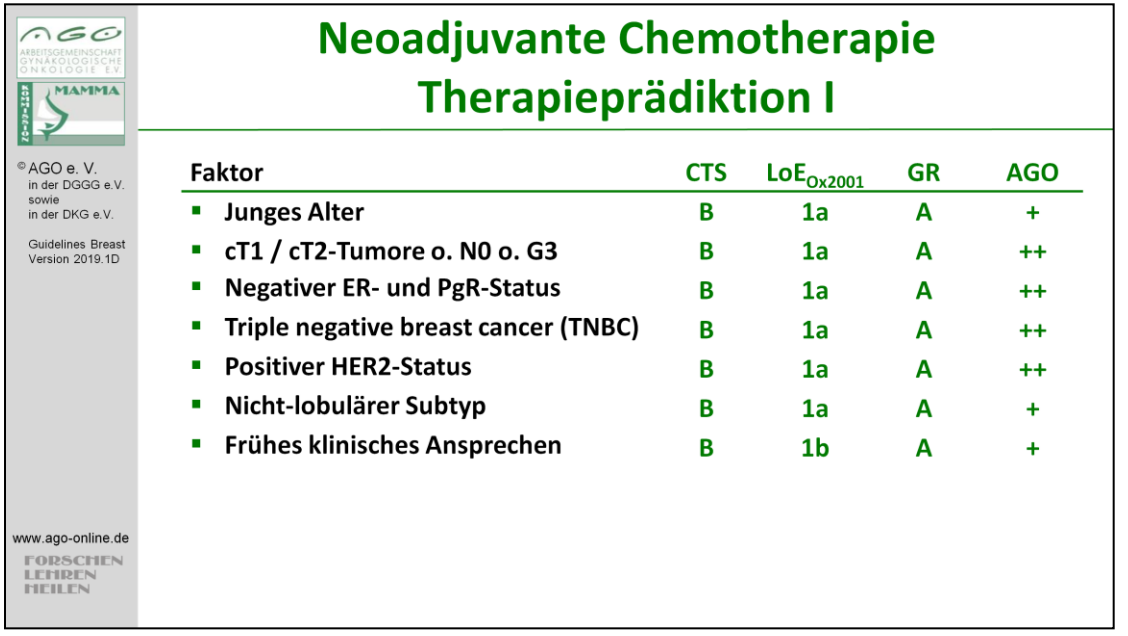

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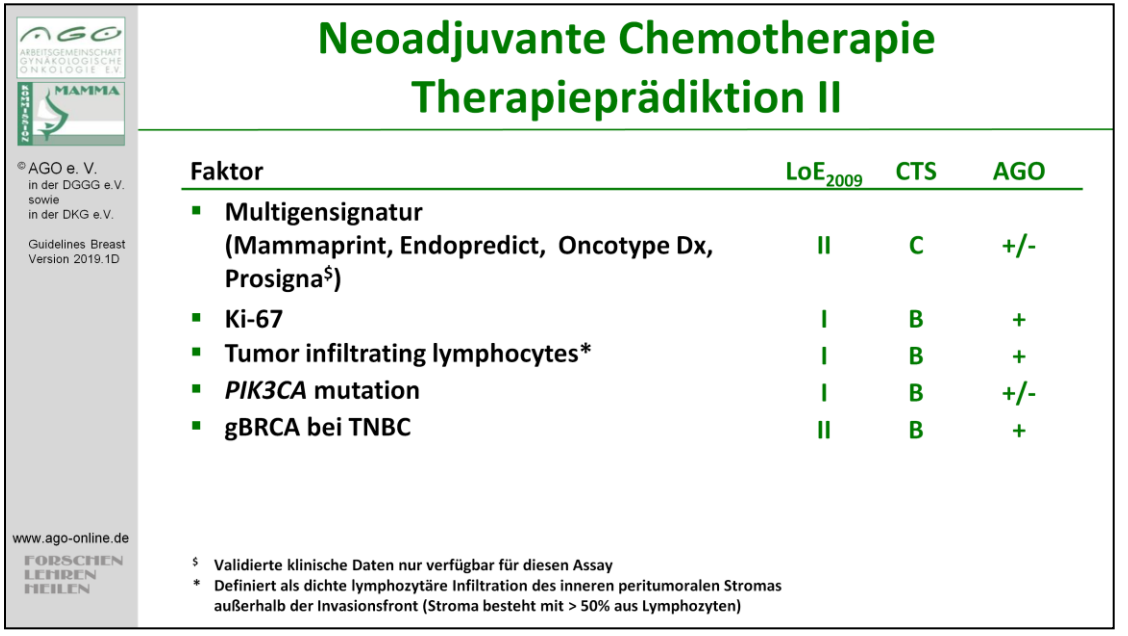

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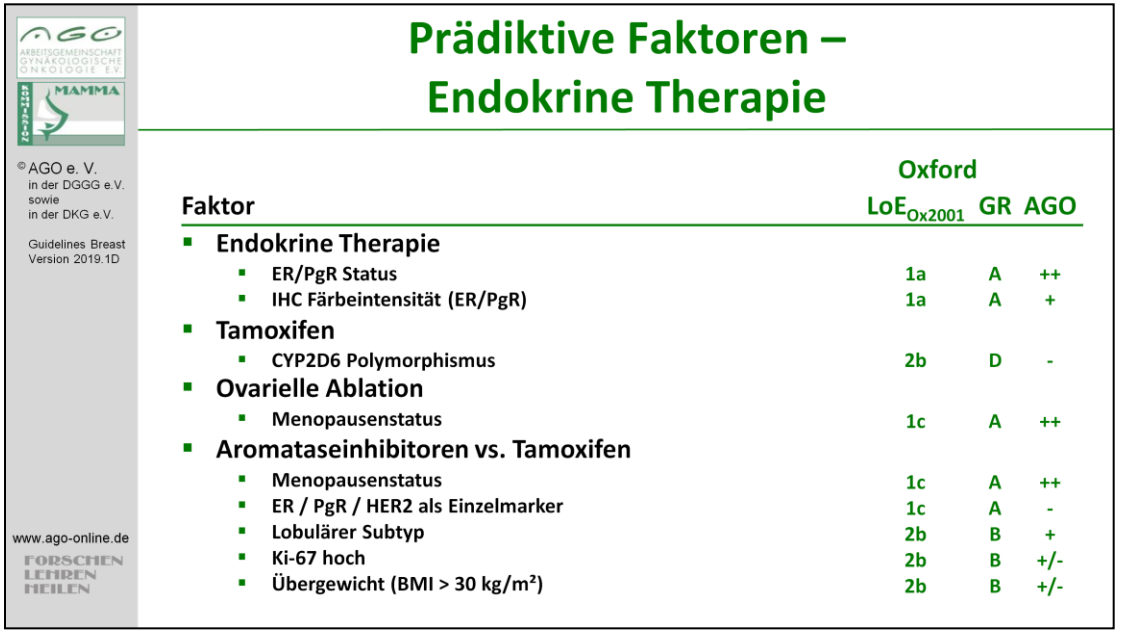

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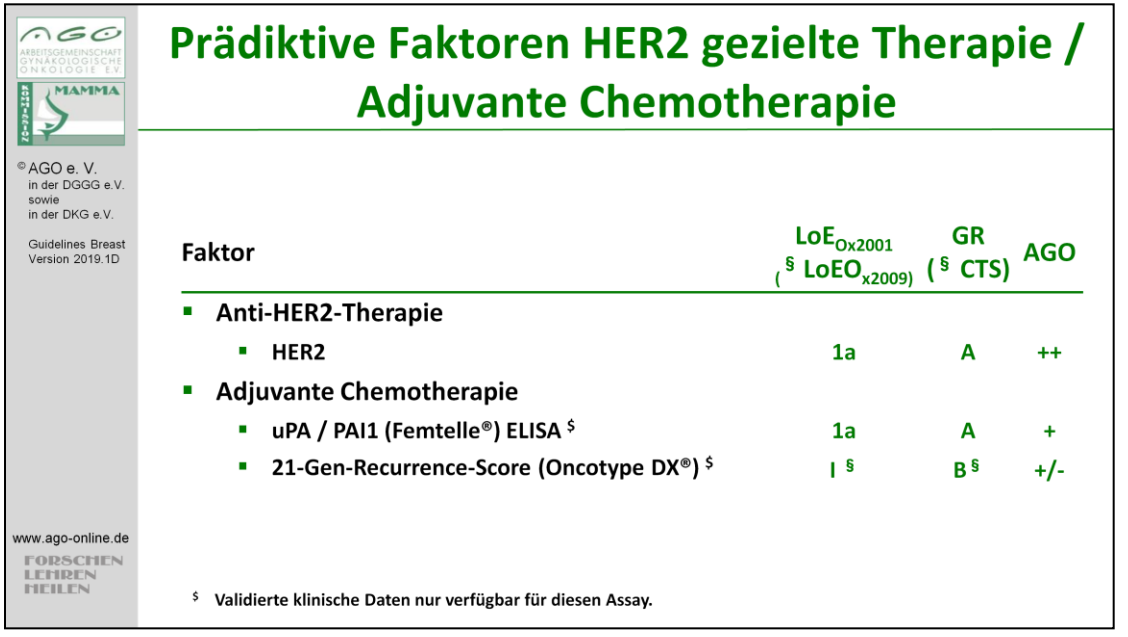

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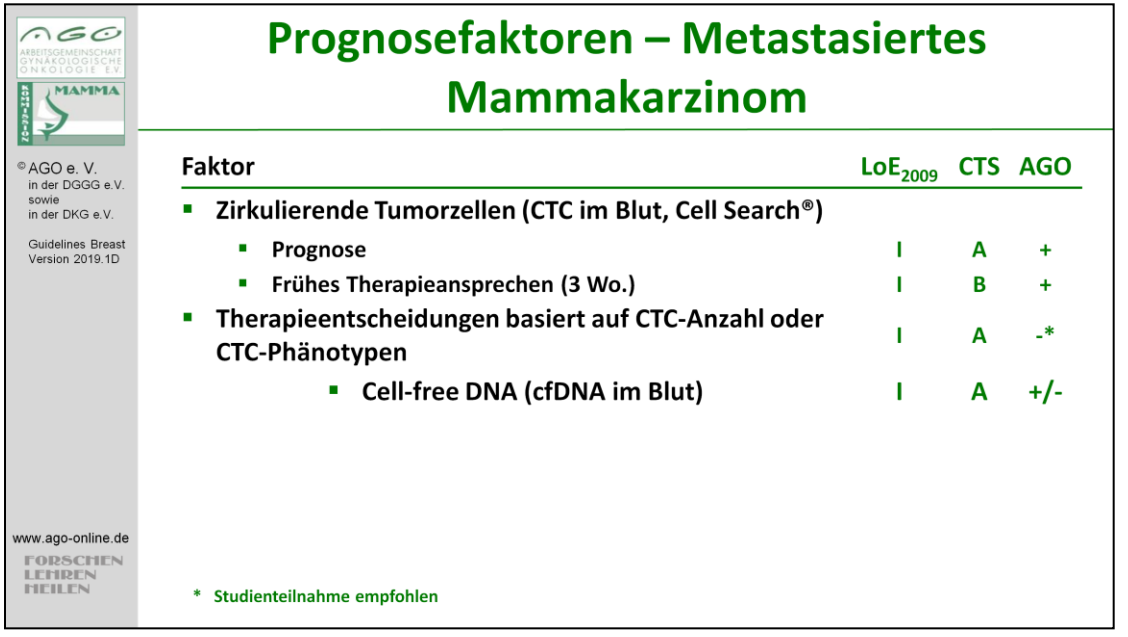

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Cell-free DNA

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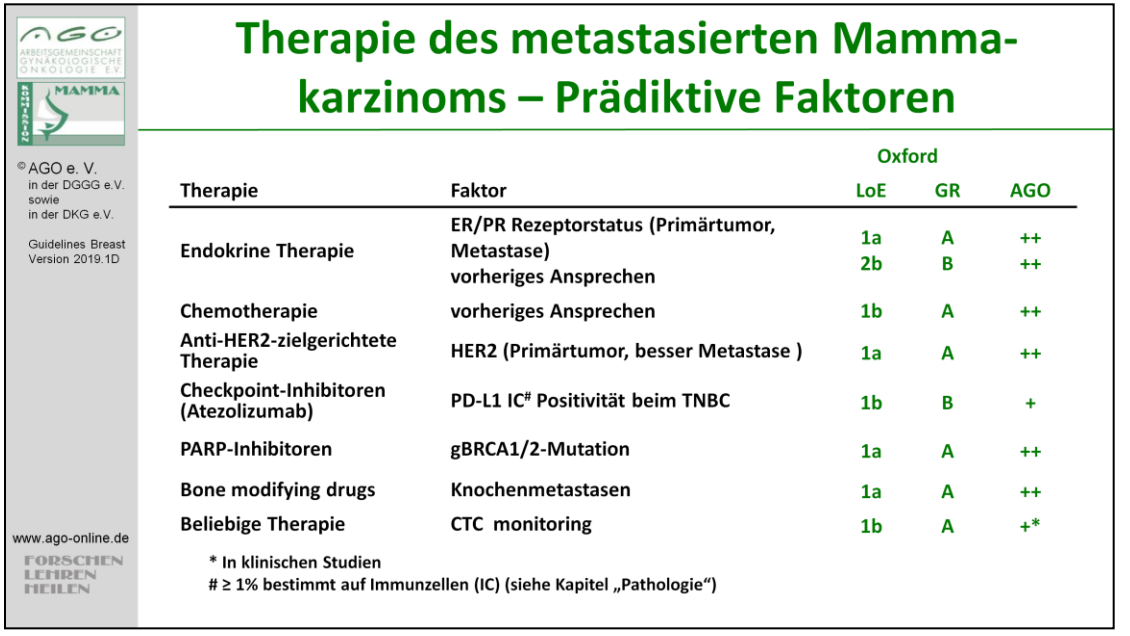

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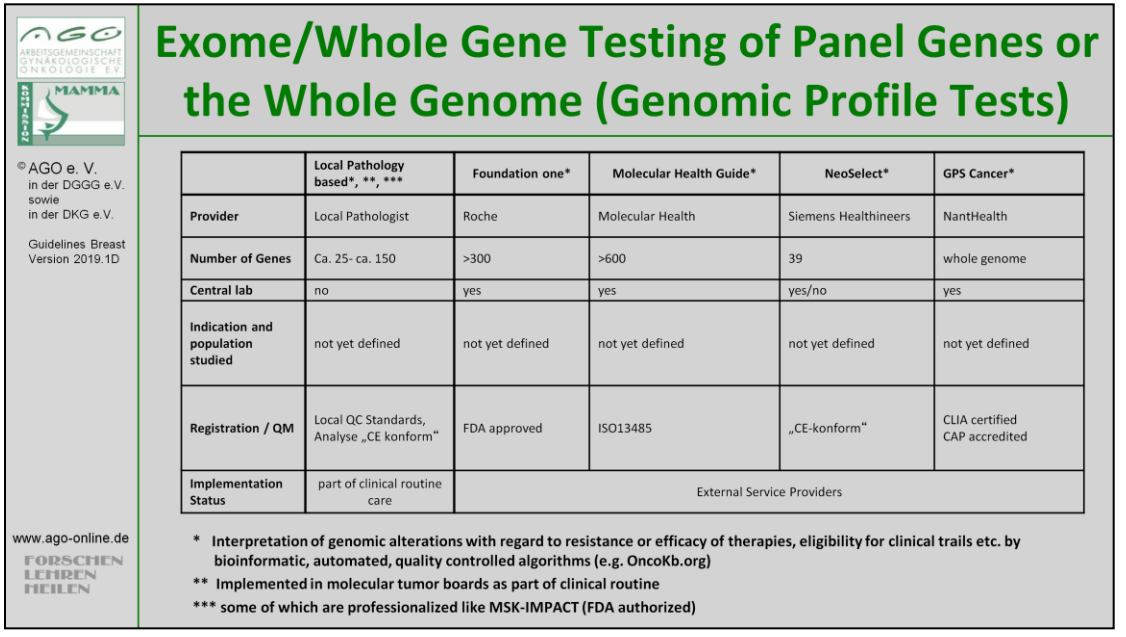

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Exome/Whole Gene Testing of Panel Genes or the Whole Genome (Genomic Profile Tests)

	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)**

<u>Commercially Available Comprehensive Molecular Profiling Tests</u>

1. http://www.newoncology.com/neoonsite.html
2. http://www.molecularhealth.com/global/
3. https://www.foundationmedicine.com/genomic-testing/foundation-one
4. http://www.gpscancer.com/

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