Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2019.1

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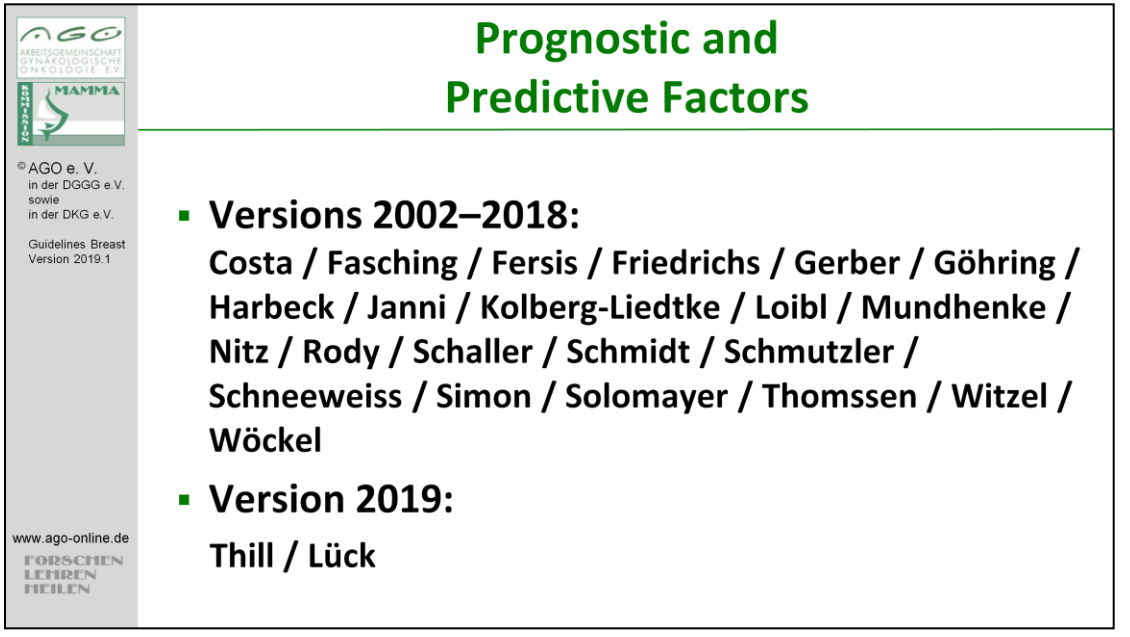
Prognostic and Predictive Factors



Data bases screened

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

Guidelines screened

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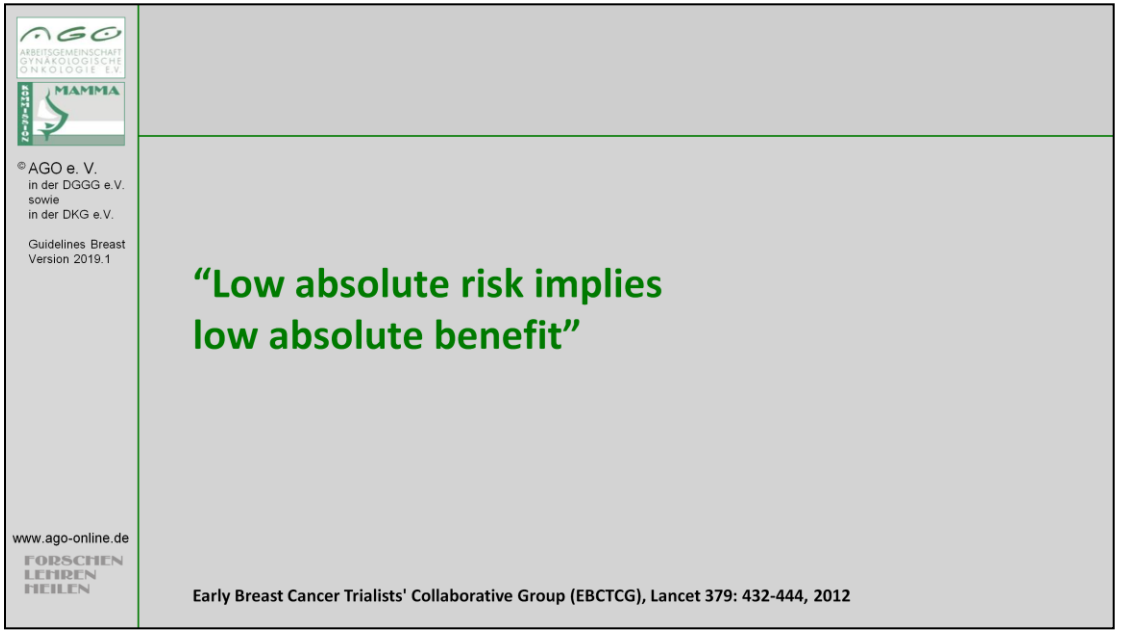
Definition

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



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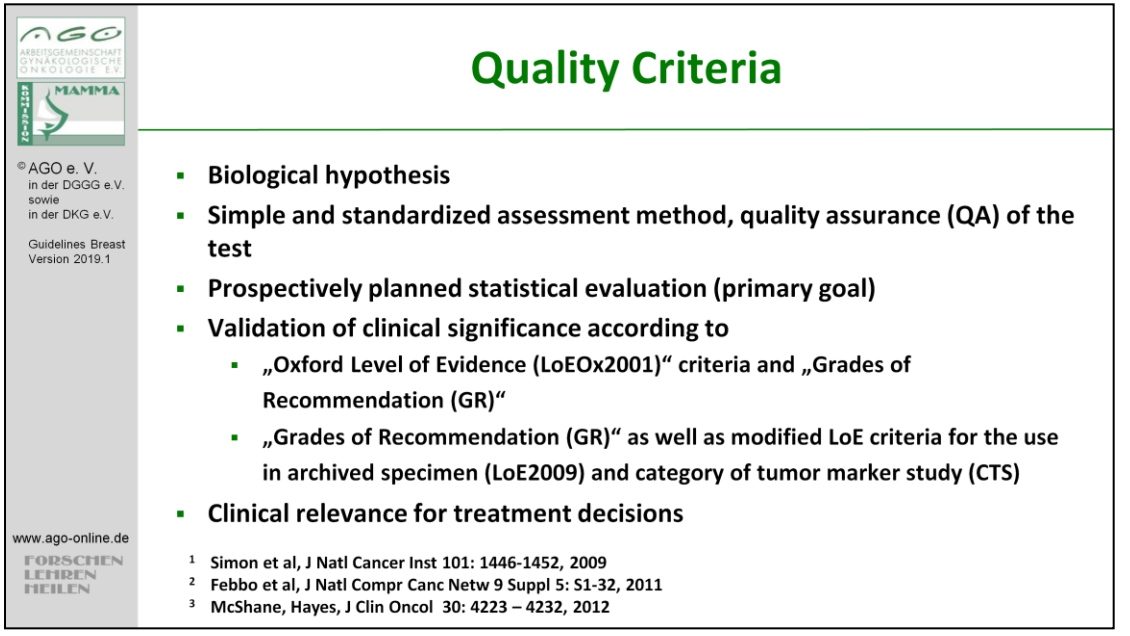

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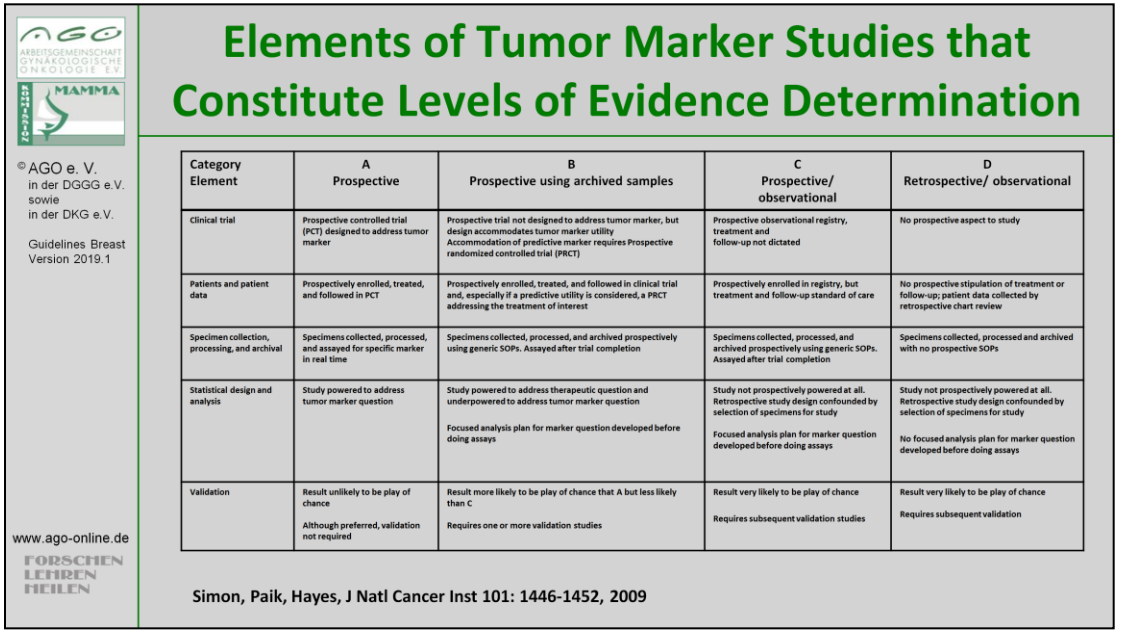

Elements of Tumor Marker Studies that Constitute Levels of Evidence Determination

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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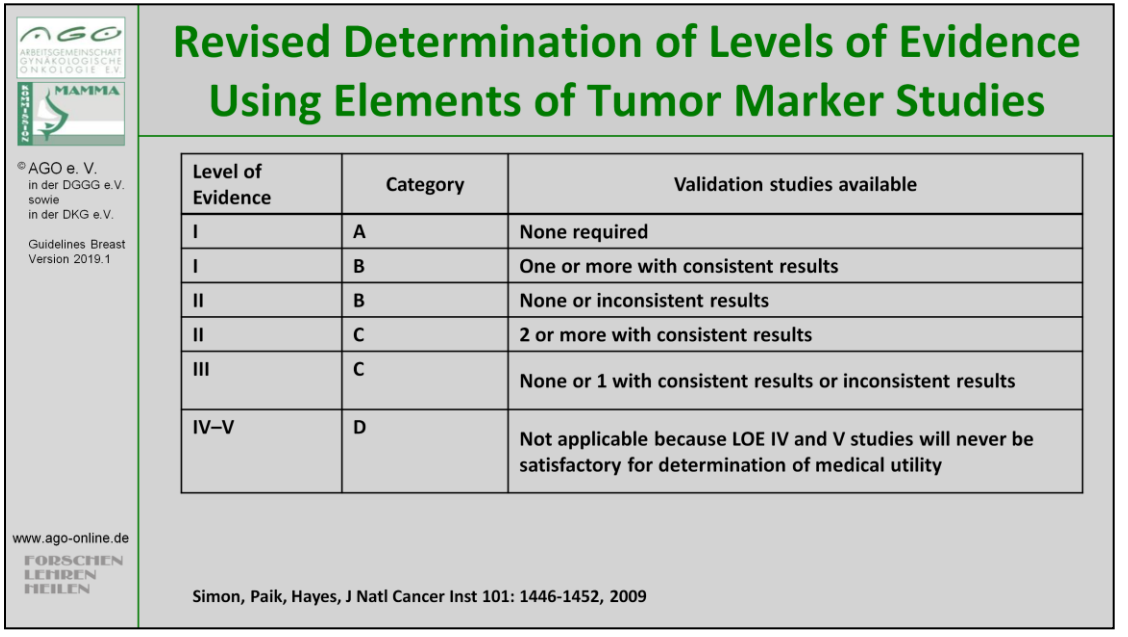

Revised Determination of Levels of Evidence Using Elements of Tumor Marker Studies

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

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

1. McShane LM, Hayes DF. Publication of tumor marker research results: the necessity for complete and transparent reporting. J. Clin. Oncol. 2012; 30(34): 4223 – 4232
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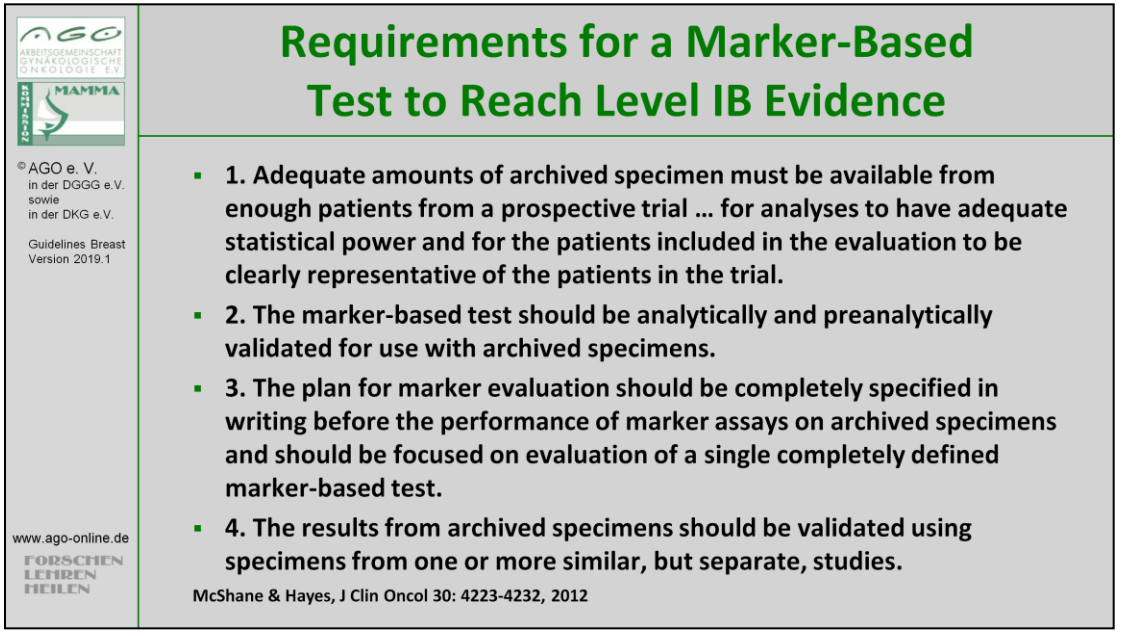

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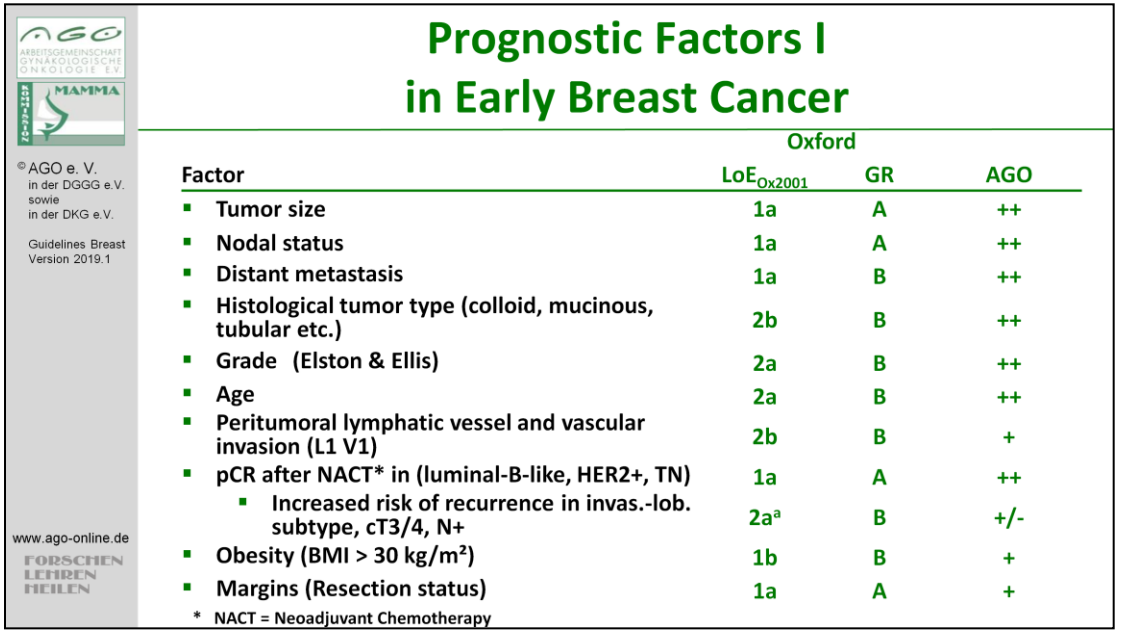

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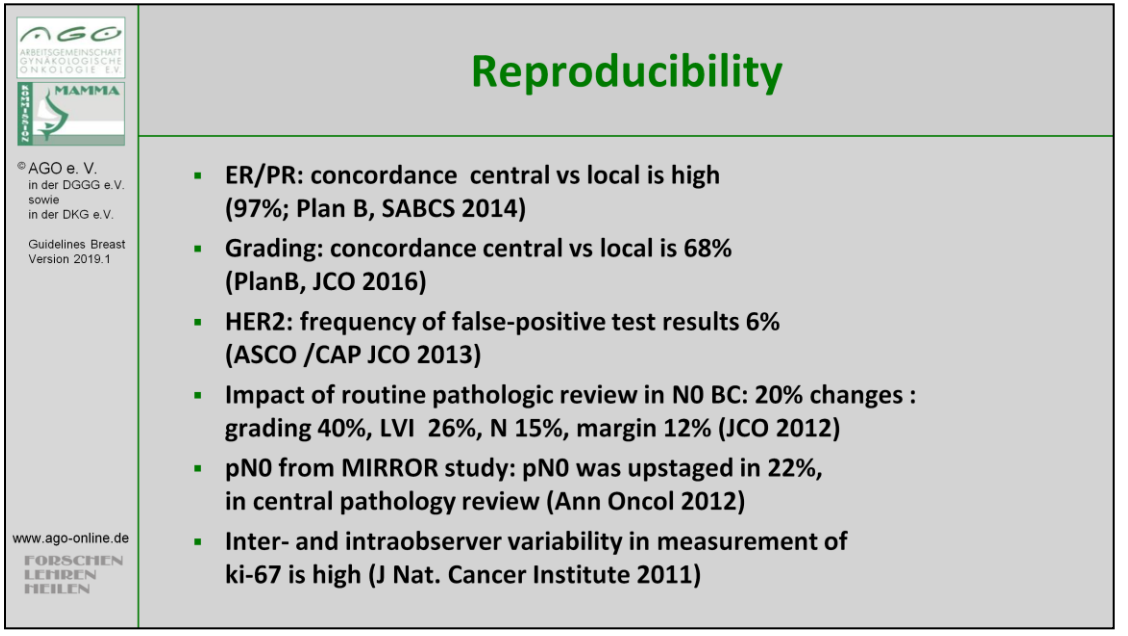

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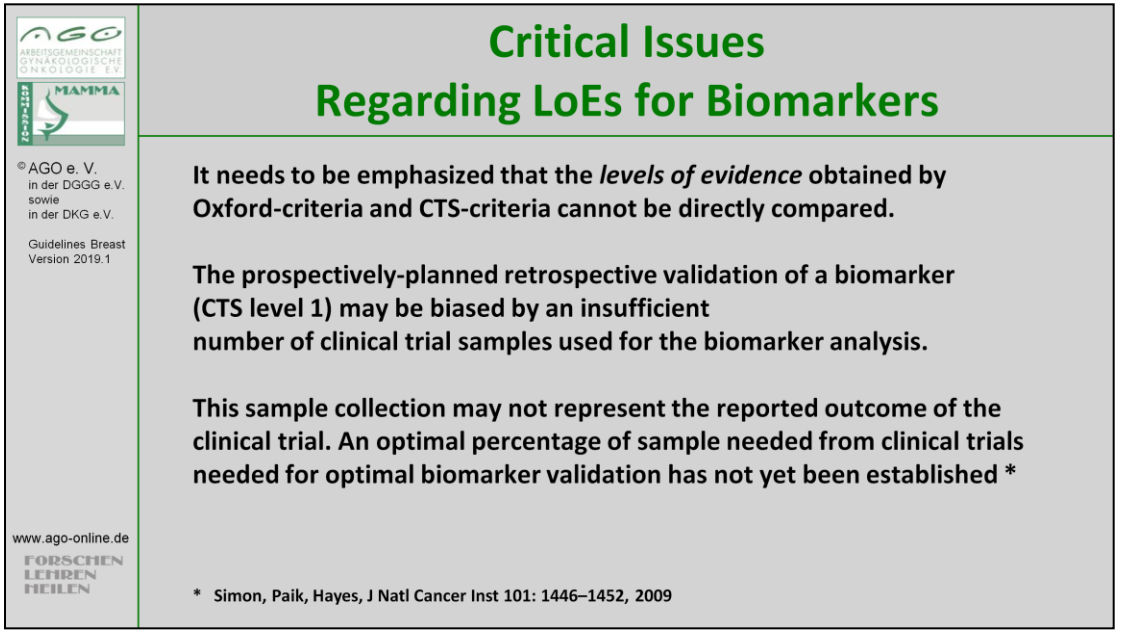

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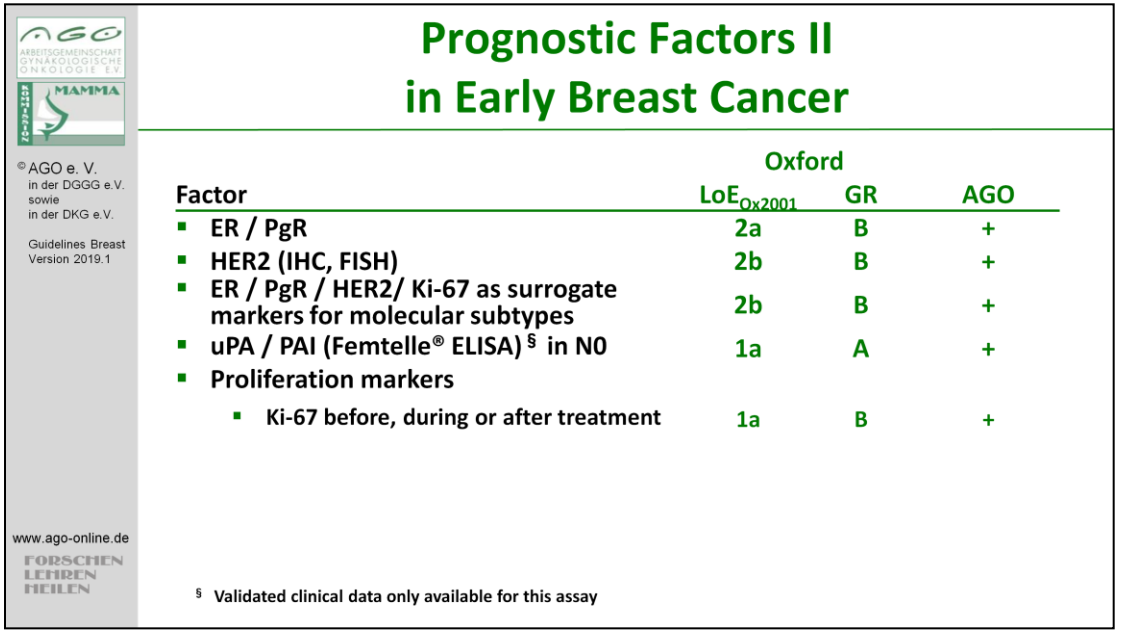

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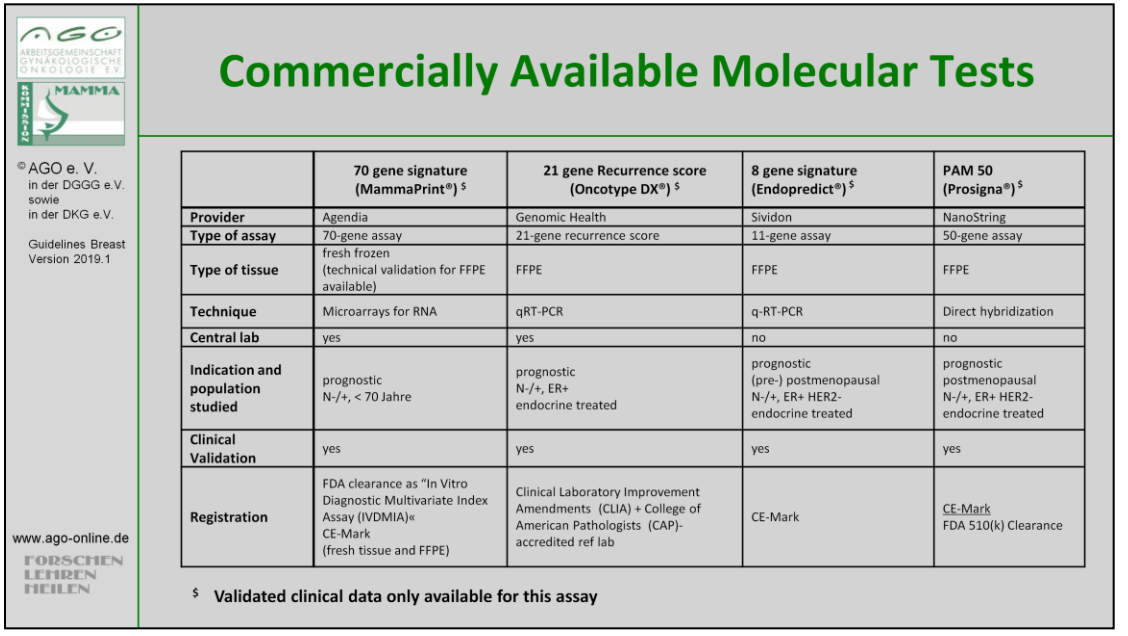

Endopredict

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Mammaprint

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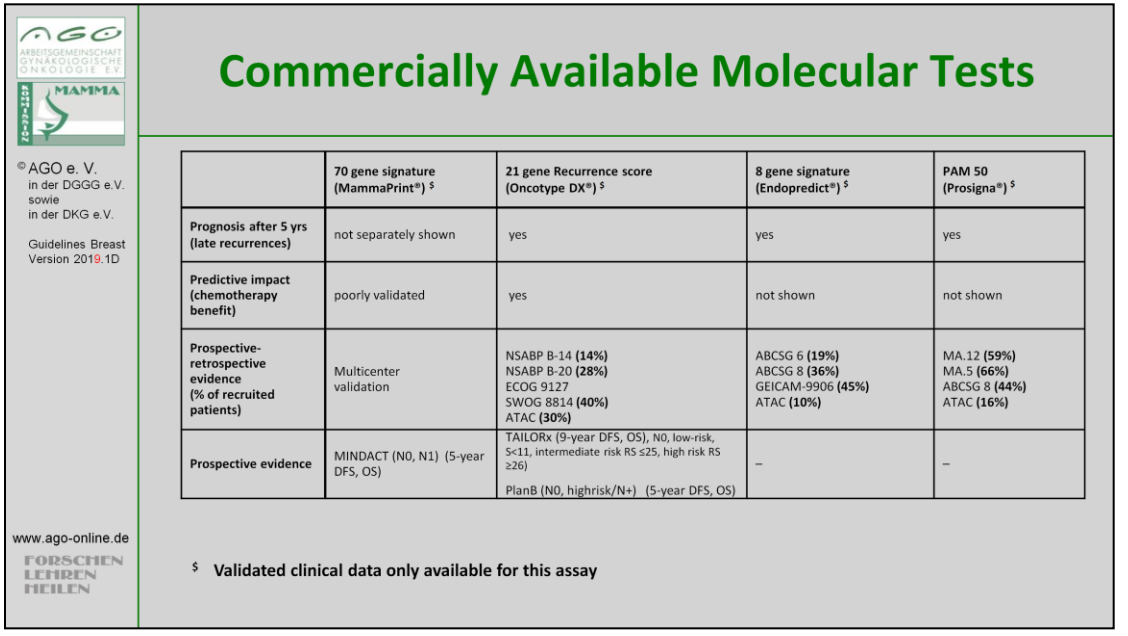

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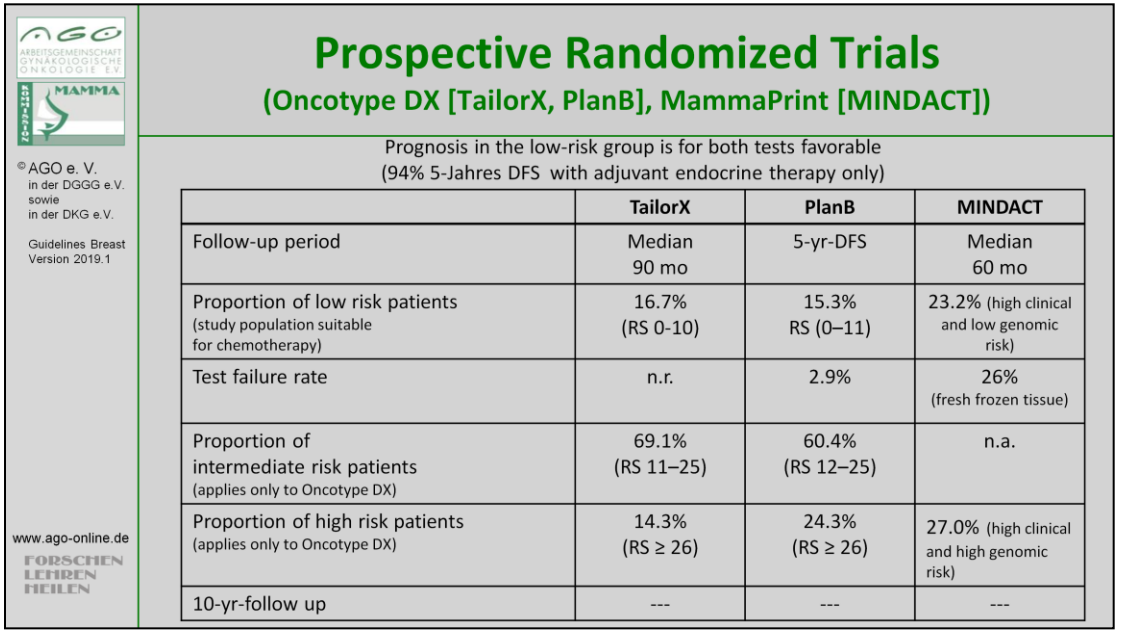

Prospective Randomized Trials

(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	---	---	---

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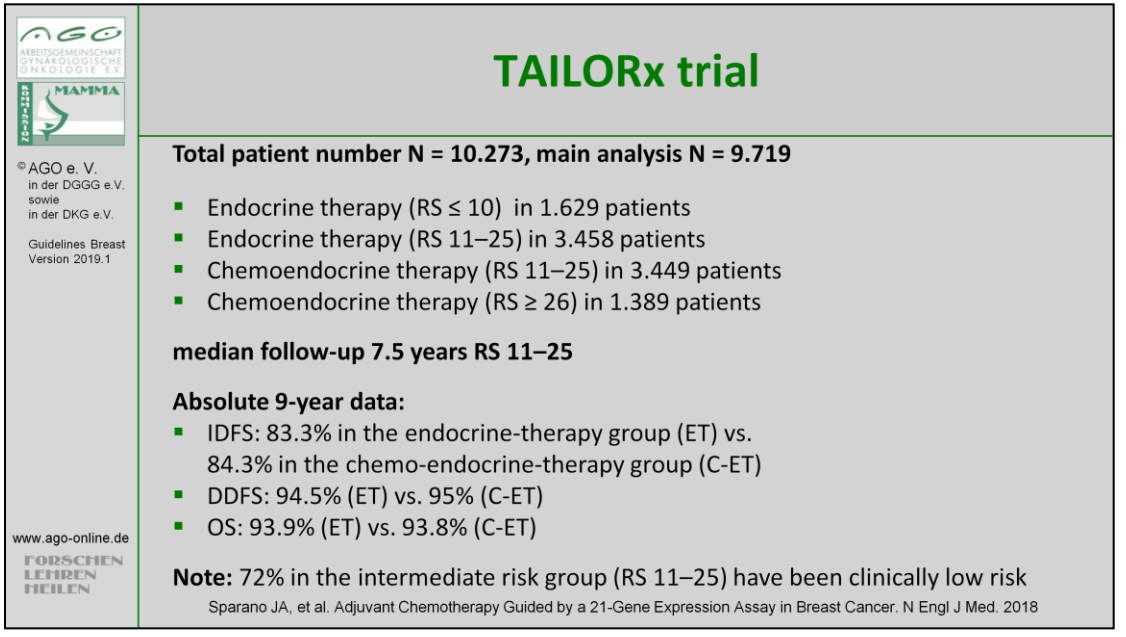

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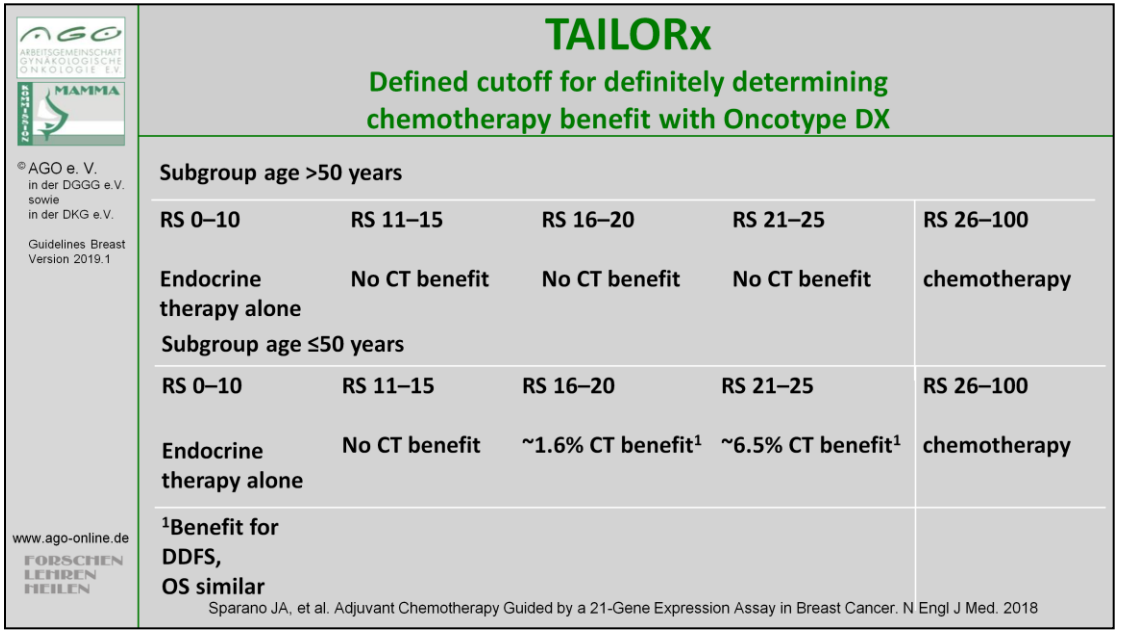

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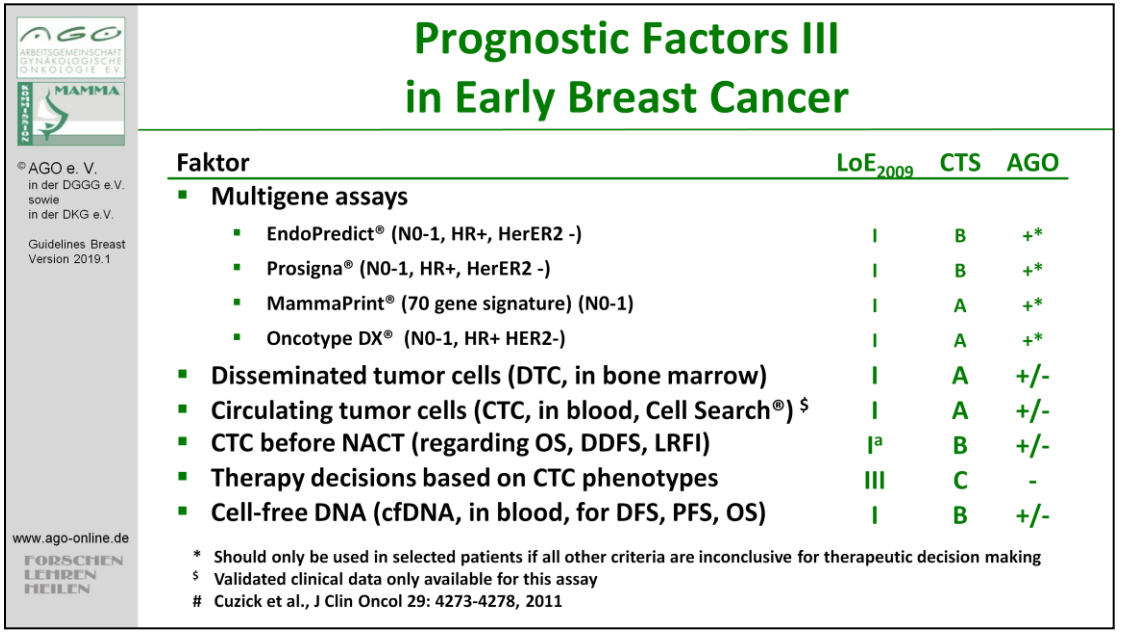

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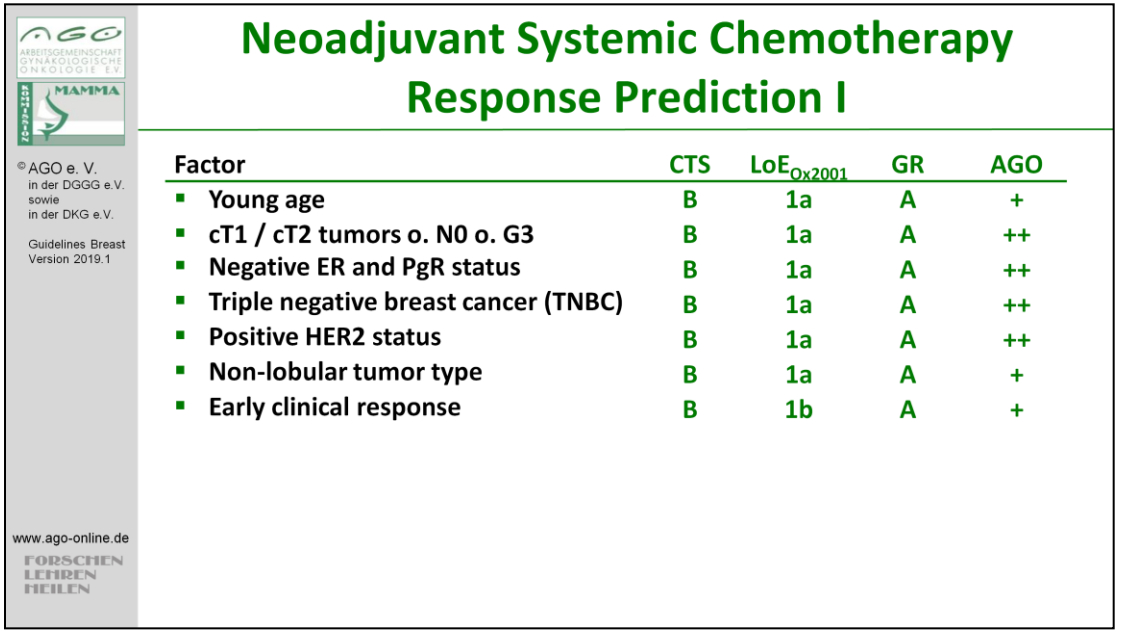

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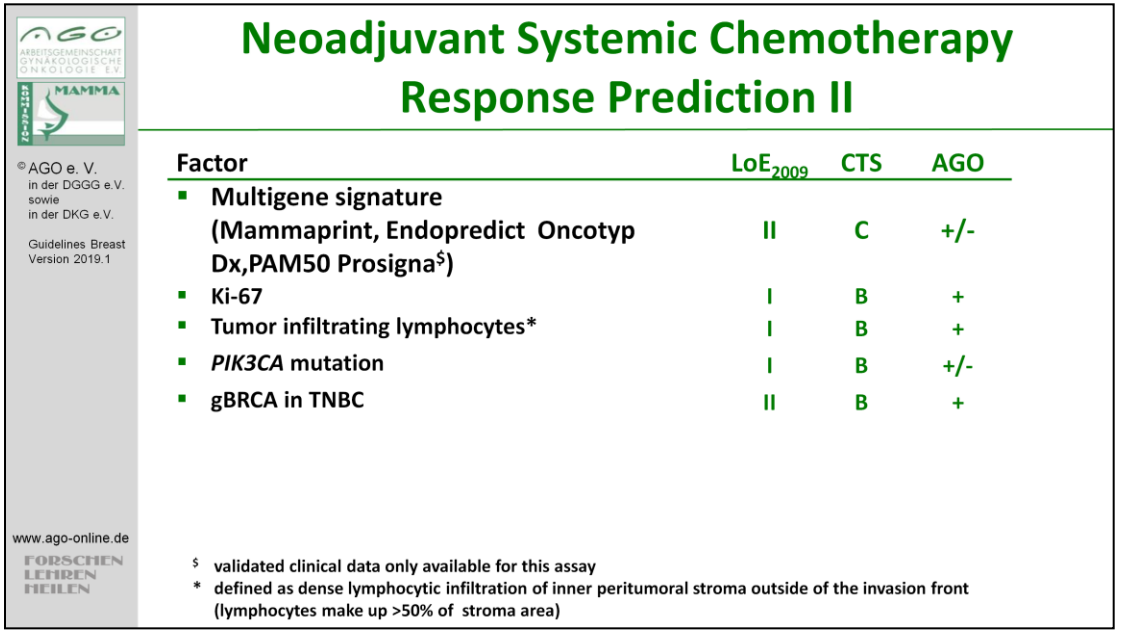

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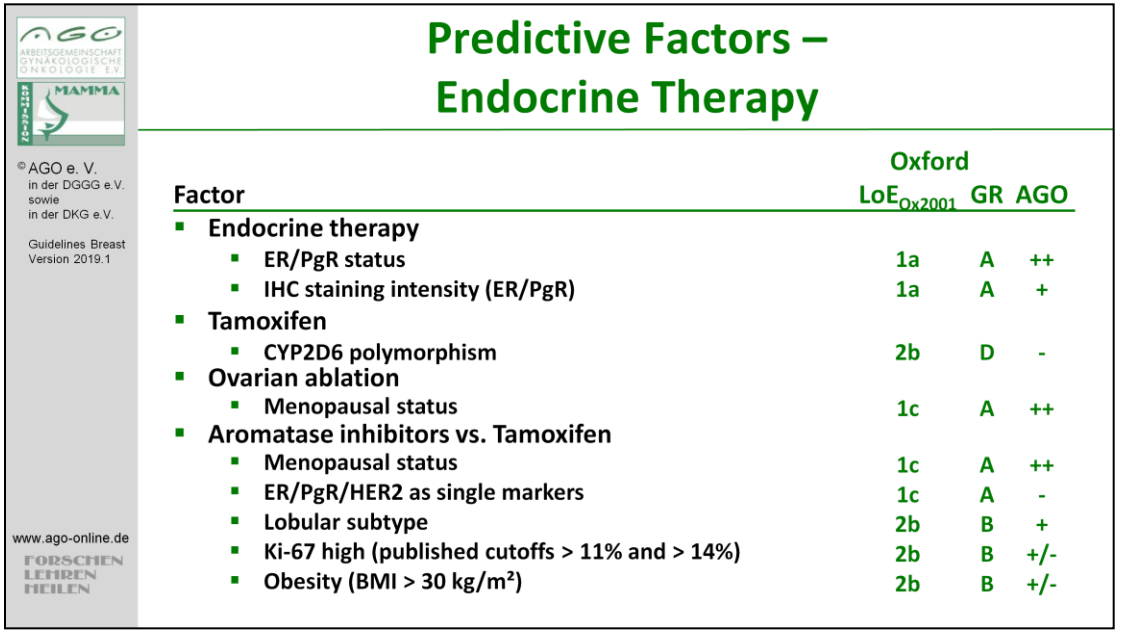

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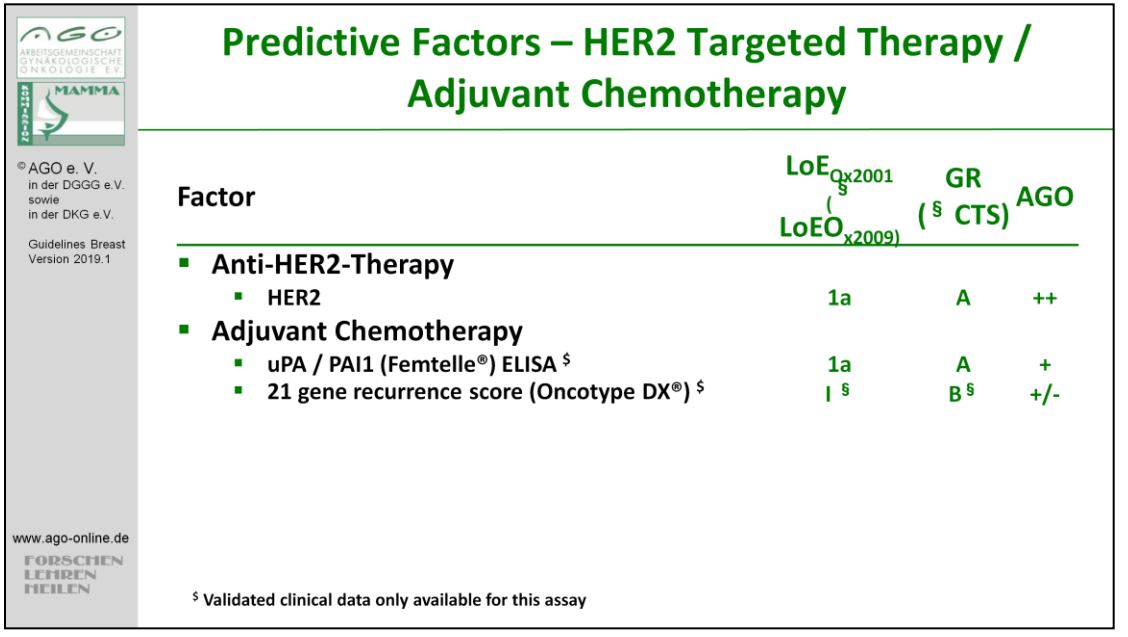

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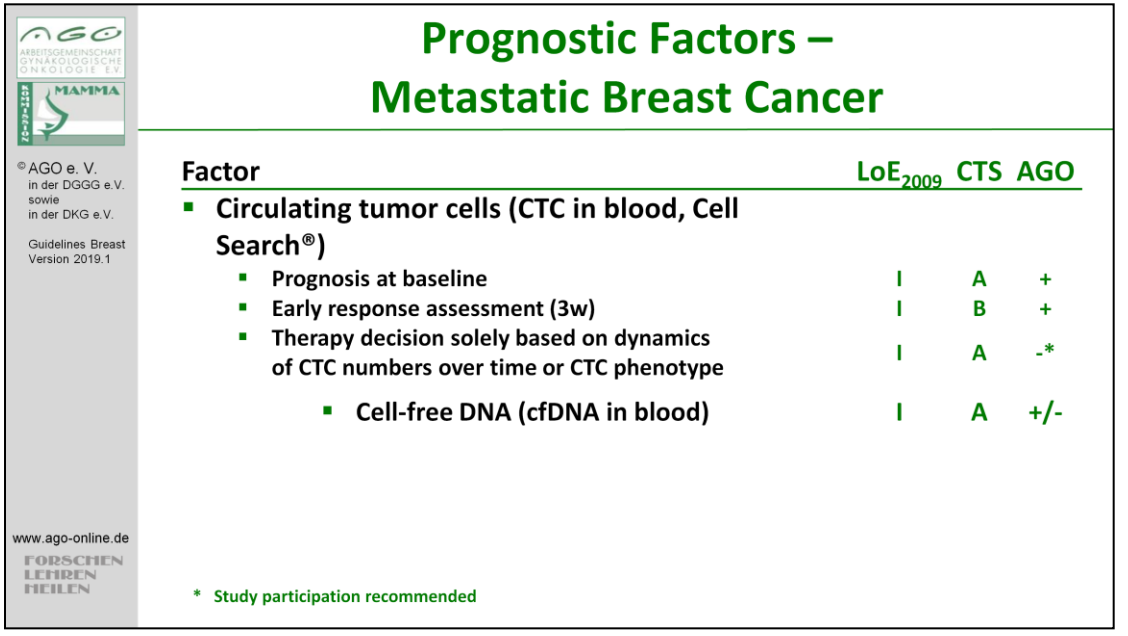

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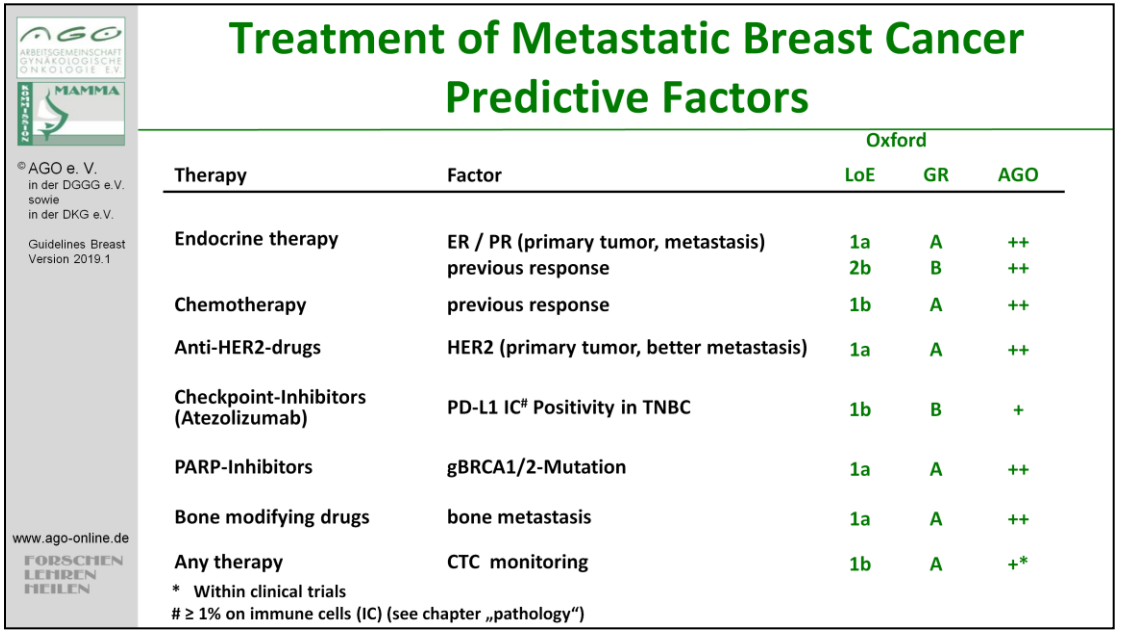

Treatment of Metastatic Breast Cancer
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Therapy	Factor	Oxford LoE	Oxford GR	AGO
Endocrine therapy	ER / PR (primary tumor, metastasis)	1a	A	++
	previous response	2b	B	++
Chemotherapy	previous response	1b	A	++
Anti-HER2-drugs	HER2 (primary tumor, better 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“)

CTC monitoring

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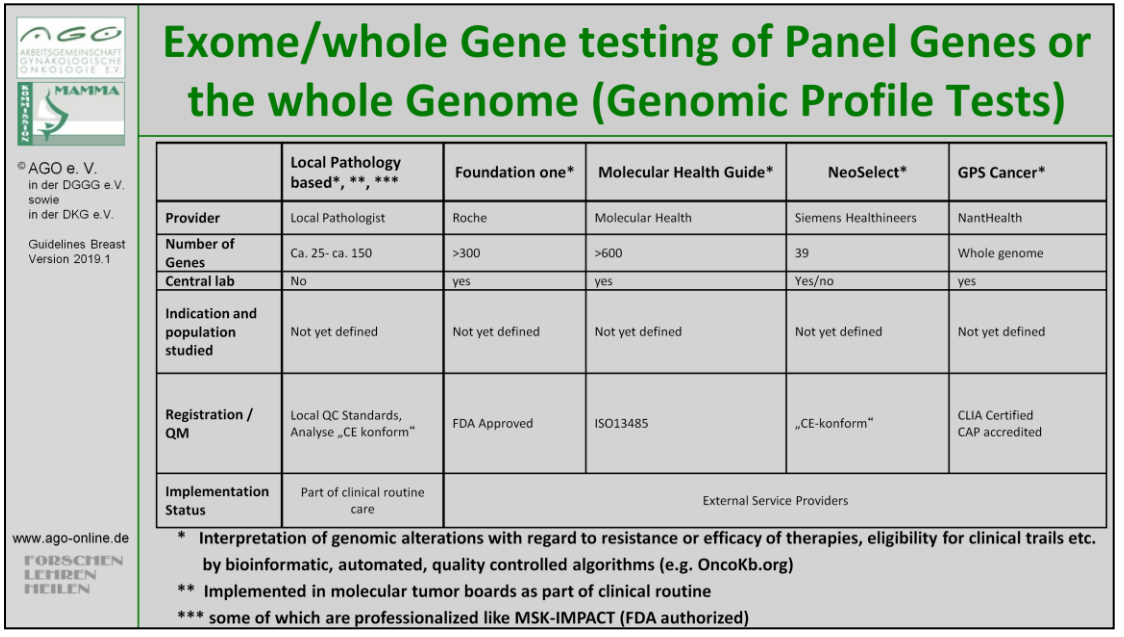


Exome/whole Gene testing of Panel Genes or the whole Genome (Genomic Profile Tests)

Guidelines Breast
Version 2019.1

	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			

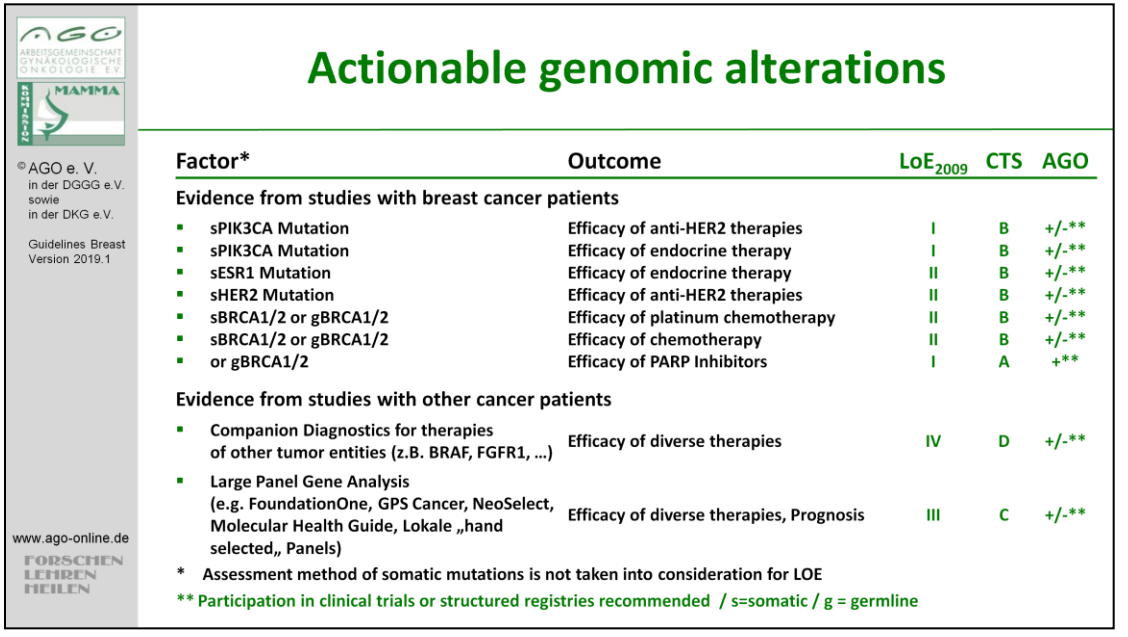
* Interpretation of genomic alterations with regard to resistance or efficacy of therapies, eligibility for clinical trails etc. by bioinformatic, automated, quality controlled algorithms (e.g. OncoKb.org)

** Implemented in molecular tumor boards as part of clinical routine

*** some of which are professionalized like MSK-IMPACT (FDA authorized)

Commercially Available Comprehensive Molecular Profiling Tests

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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PIK3CA

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