Guidelines Breast
Version 2022.1E

FORSCHEN
LEHREN
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Breast Cancer Risk, Genetics and Prevention

Guidelines Breast
Version 2022.1E

Breast Cancer Risk and Prevention

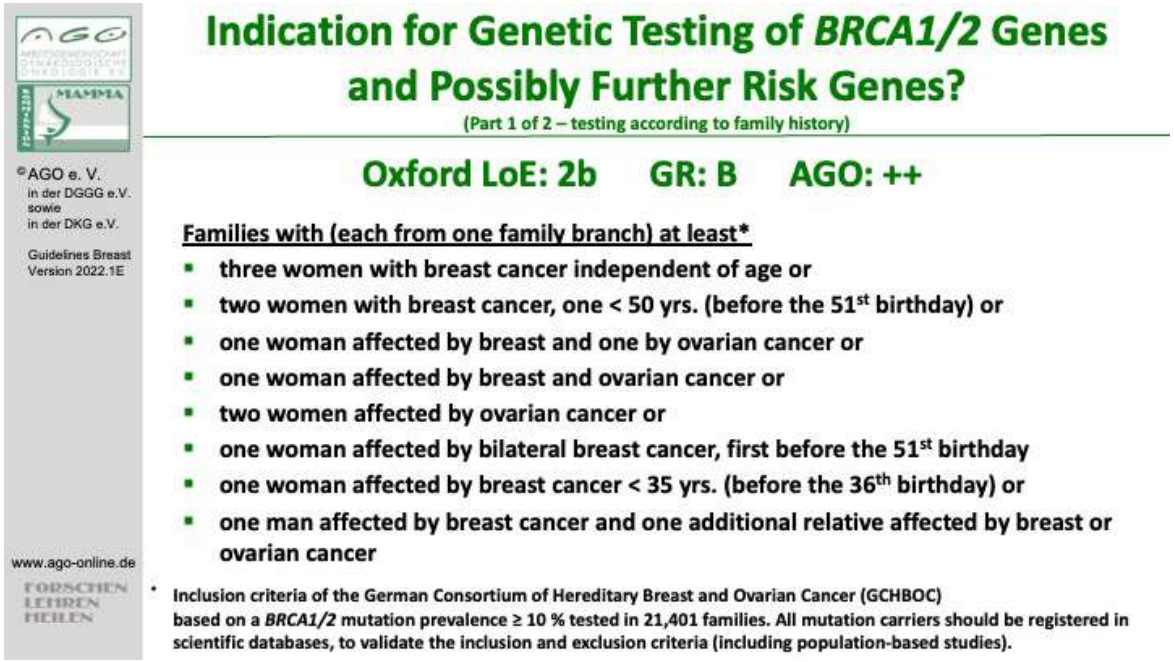
- **Versions 2003–2021:**
  Albert / Bischoff / Blohmer / Ditsch / Fasching / Fehm / Kiechle / Maass / Müller-Schimpfle / Mundhenke / Park-Simon / Rhiem / Rody / Schmidt / Schmutzler / Stickeler / Thomssen / Witzel

- **Version 2022:**
  Dall / Ditsch / Gerber / Rhiem

Principles of Prevention

- **Women at increased risk for breast cancer are not considered *patients* but *healthy women* or *counselees.***
- **A comprehensive informed consent taking into consideration all potential side effects and risks is warranted prior to offering preventive measures.**
- **Highest priority: „First, do no harm!“**

(Primum nil nocere)



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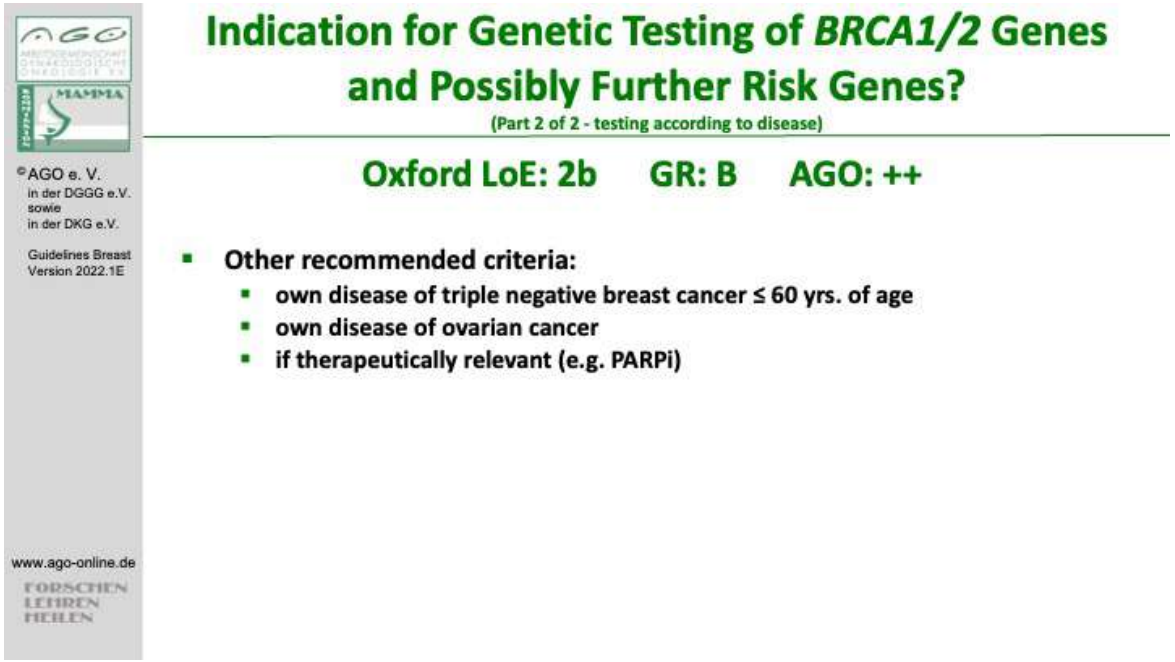

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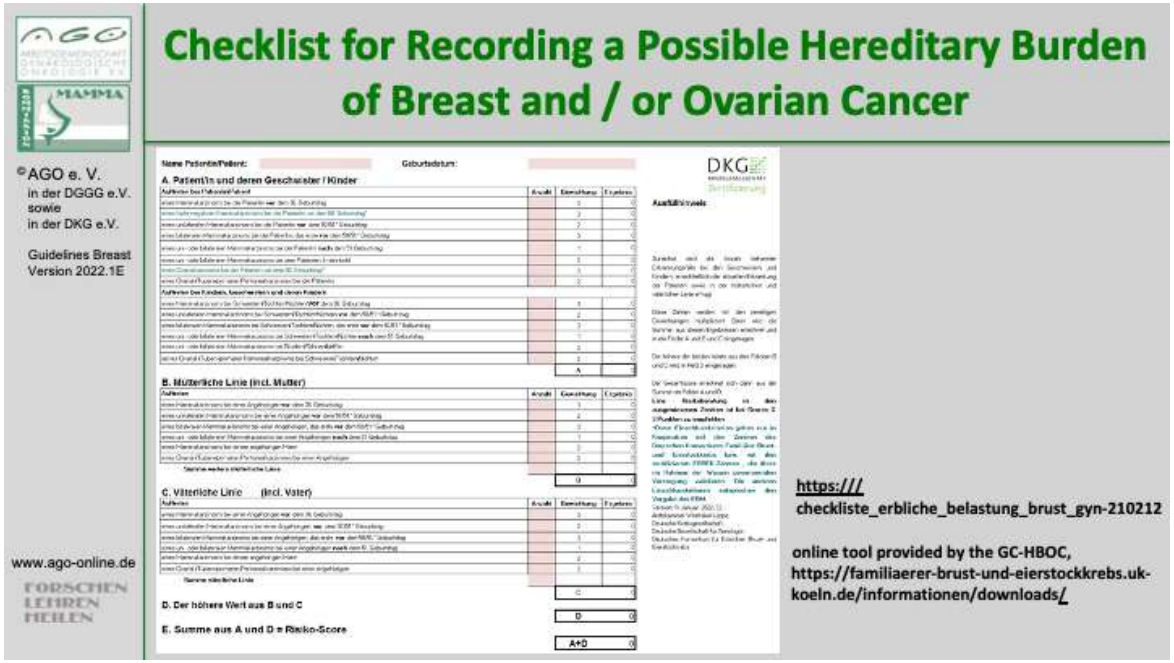

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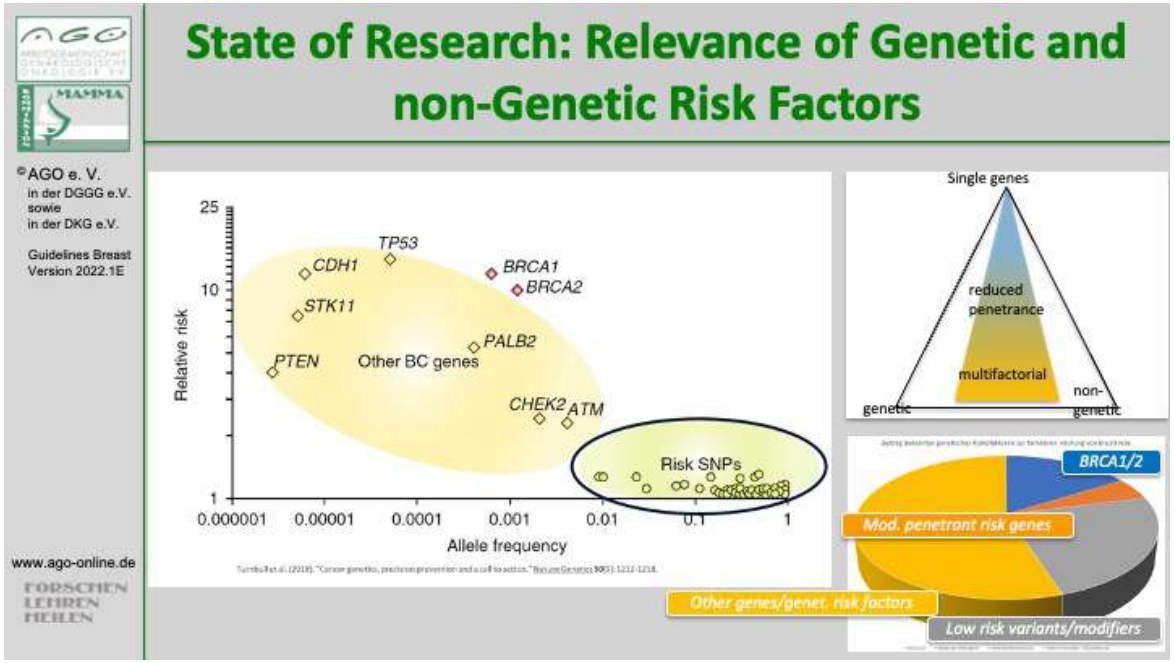

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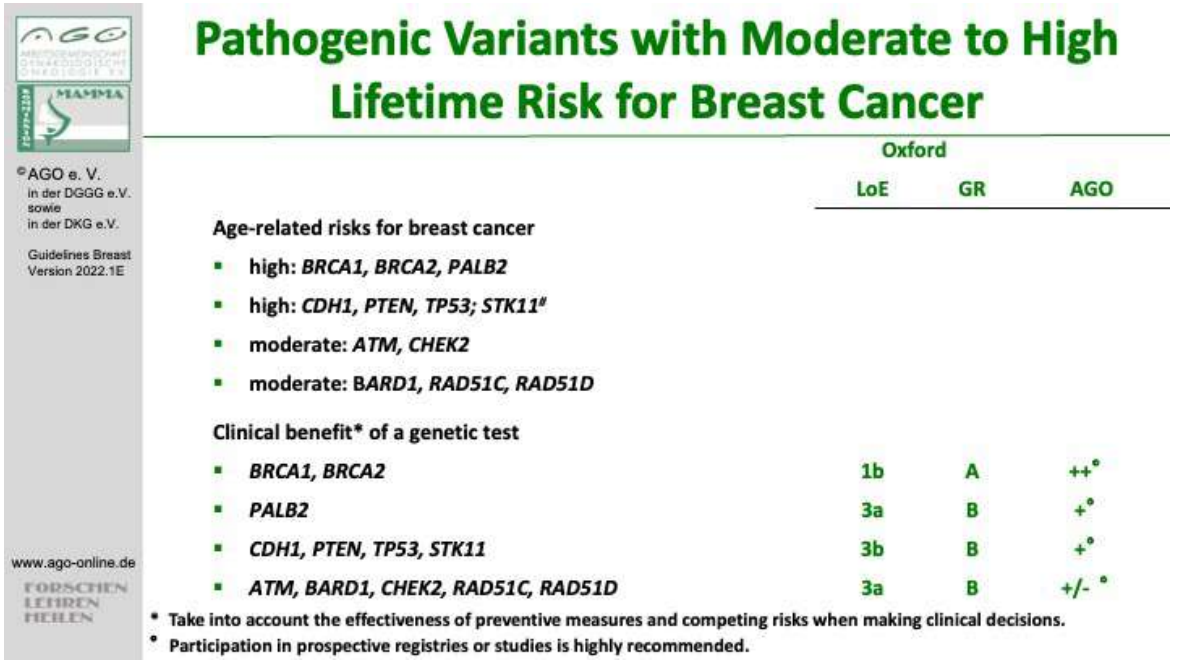

Pathogenic Variants with Moderate to High Lifetime Risk for Breast Cancer

	Oxford LoE	Oxford GR	Oxford AGO
Age-related risks for breast cancer			
▪ high: ***BRCA1, BRCA2, PALB2***			
▪ high: ***CDH1, PTEN, TP53; STK11#***			
▪ moderate: ***ATM, CHEK2***			
▪ moderate: B***ARD1, RAD51C, RAD51D***			
Clinical benefit* of a genetic test			
▪ ***BRCA1, BRCA2***	1b	A	++°
▪ ***PALB2***	3a	B	+°
▪ ***CDH1, PTEN, TP53, STK11***	3b	B	+°
▪ ***ATM, BARD1, CHEK2, RAD51C, RAD51D***	3a	B	+/- °

* Take into account the effectiveness of preventive measures and competing risks when making clinical decisions.
° Participation in prospective registries or studies is highly recommended.

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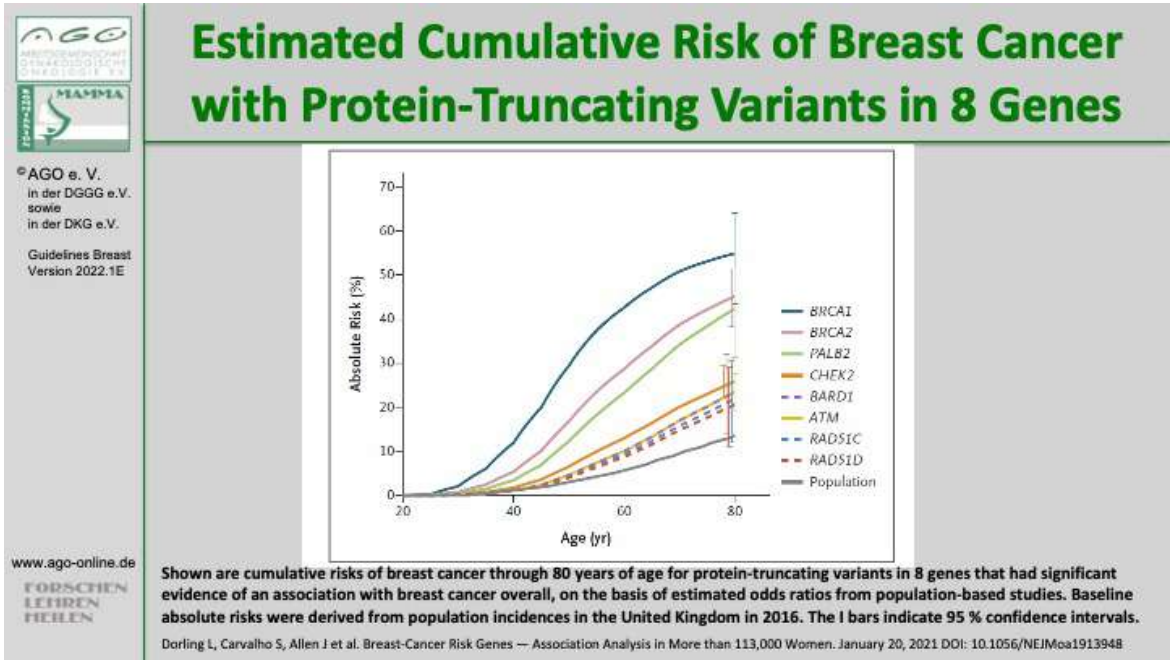
Breast Cancer Risk Category

Breast cancer risk category

	Near population risk of breast cancer	Moderate risk of breast cancer	High risk of breast cancer
Lifetime risk from age 20	Less than 17%	Greater than 17% but less than 30%	30% or greater
Risk between ages 40 and 50	Less than 3%	3 to 8%	Greater than 8%

NICE (National Institute for Health and Care Excellence) guidance: Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer
Clinical guideline [CG164] Published: 25 June 2013 Last updated: 20 November 2019



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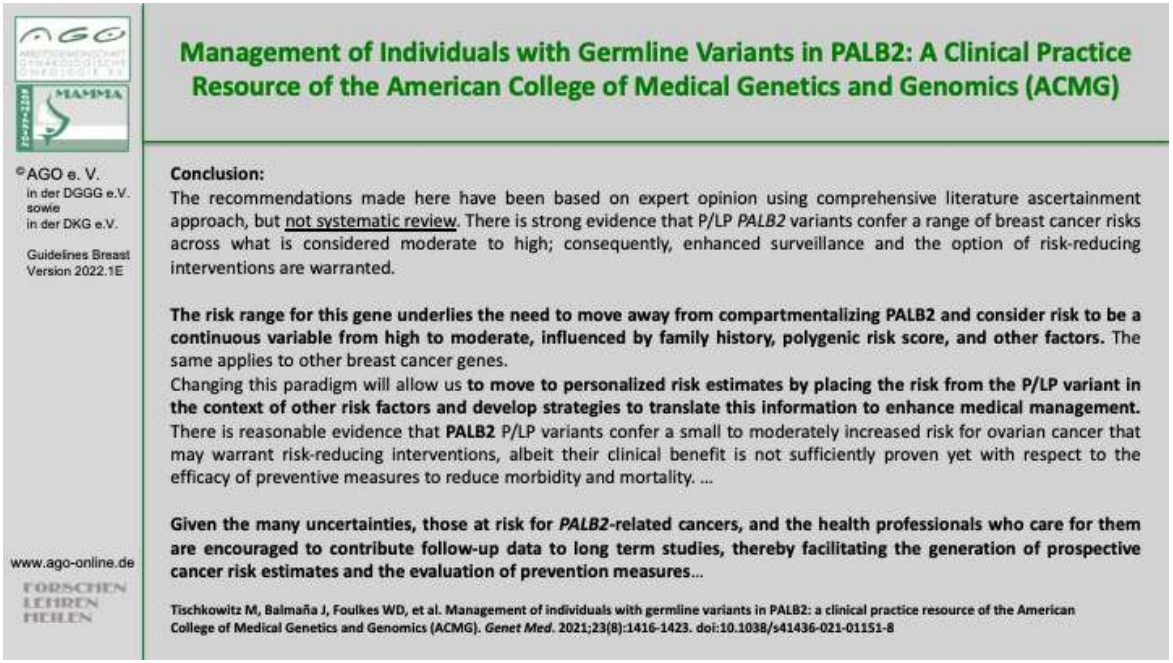

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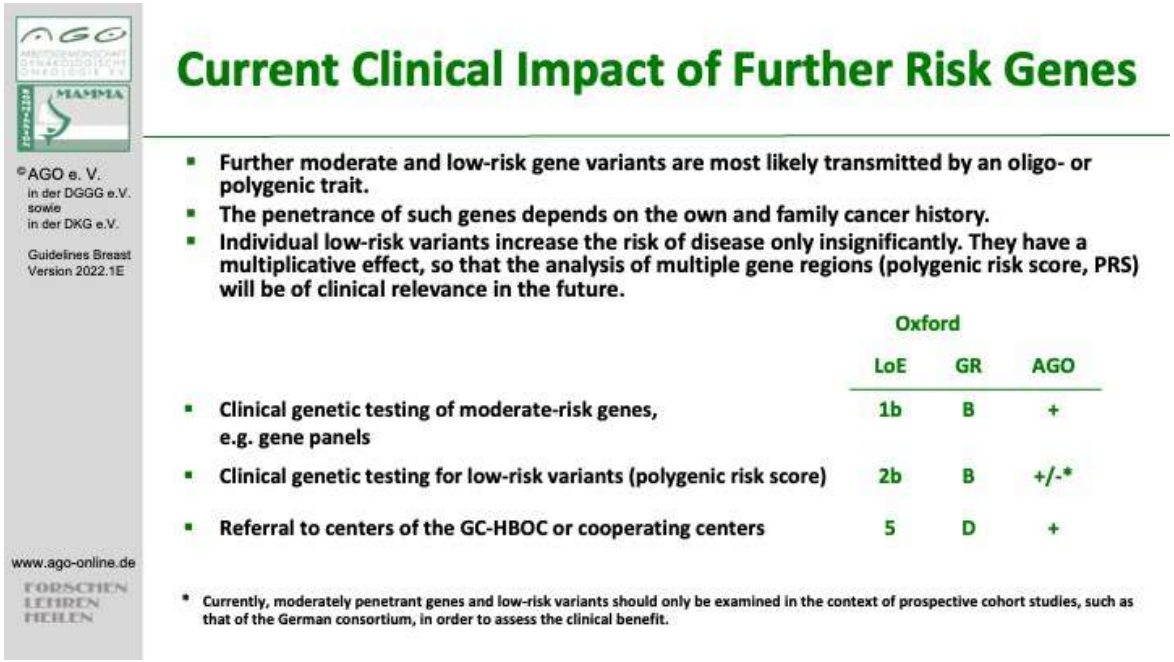

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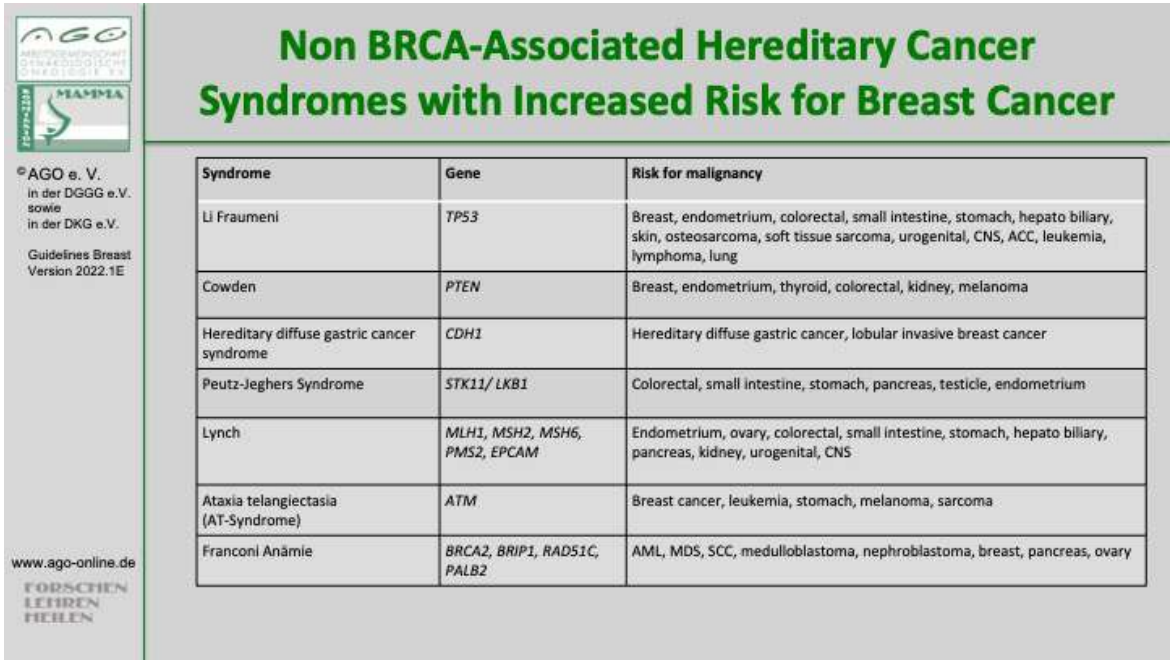

Non BRCA-Associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer

Syndrome	Gene	Risk for malignancy
Li Fraumeni	*TP53*	Breast, endometrium, colorectal, small intestine, stomach, hepato biliary, skin, osteosarcoma, soft tissue sarcoma, urogenital, CNS, ACC, leukemia, lymphoma, lung
Cowden	*PTEN*	Breast, endometrium, thyroid, colorectal, kidney, melanoma
Hereditary diffuse gastric cancer syndrome	*CDH1*	Hereditary diffuse gastric cancer, lobular invasive breast cancer
Peutz-Jeghers Syndrome	*STK11/ LKB1*	Colorectal, small intestine, stomach, pancreas, testicle, endometrium
Lynch	*MLH1, MSH2, MSH6, PMS2, EPCAM*	Endometrium, ovary, colorectal, small intestine, stomach, hepato billiary, pancreas, kidney, urogenital, CNS
Ataxia telangiectasia (AT-Syndrome)	*ATM*	Breast cancer, leukemia, stomach, melanoma, sarcoma
Franconi Anämie	*BRCA2, BRIP1, RAD51C, PALB2*	AML, MDS, SCC, medulloblastoma, nephroblastoma, breast, pancreas, ovary

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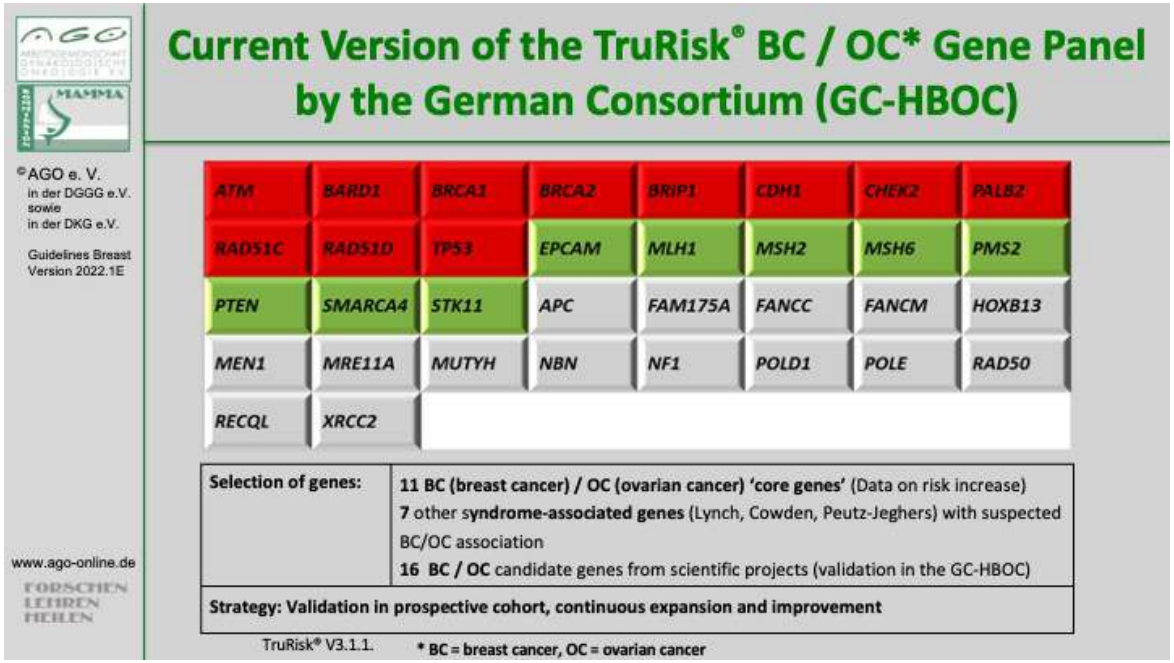
Current Version of the TruRisk® BC / OC* Gene Panel by the German Consortium (GC-HBOC)
©AGO e. V.
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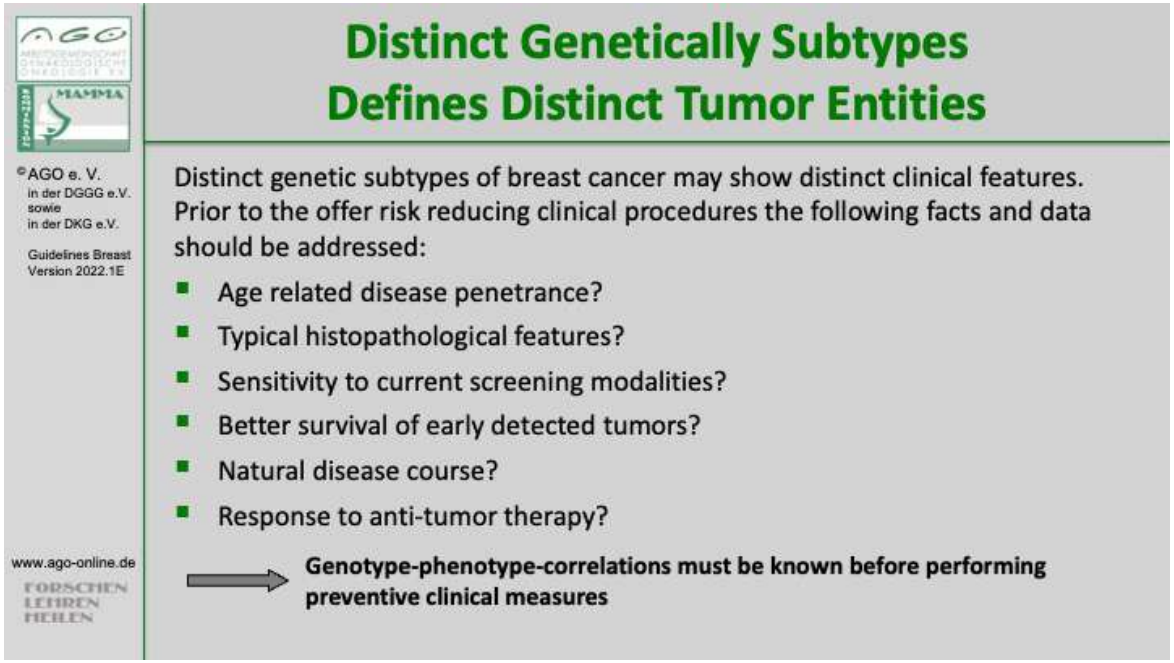
Guidelines Breast
Version 2022.1E
ATM
BARD1
BRCA1
BRCA2
BRIP1
CDH1
CHEK2
PALB2
RAD51C
RAD51D
TP53
EPCAM
MLH1
MSH2
MSH6
PMS2
PTEN
SMARCA4
STK11
APC
FAM175A
FANCC
FANCM
HOXB13
MEN1
MRE11A
MUTYH
NBN
NF1
POLD1
POLE
RAD50
RECQL
XRCC2
Selection of genes:
11 BC (breast cancer) / OC (ovarian cancer) 'core genes' (Data on risk increase)
7 other syndrome-associated genes (Lynch, Cowden, Peutz-Jeghers) with suspected BC/OC association
16 BC / OC candidate genes from scientific projects (validation in the GC-HBOC)
Strategy: Validation in prospective cohort, continuous expansion and improvement
www.ago-online.de
FORSCHEN
LEHREN
HEILEN
TruRisk® V3.1.1.
* BC = breast cancer, OC = ovarian cancer



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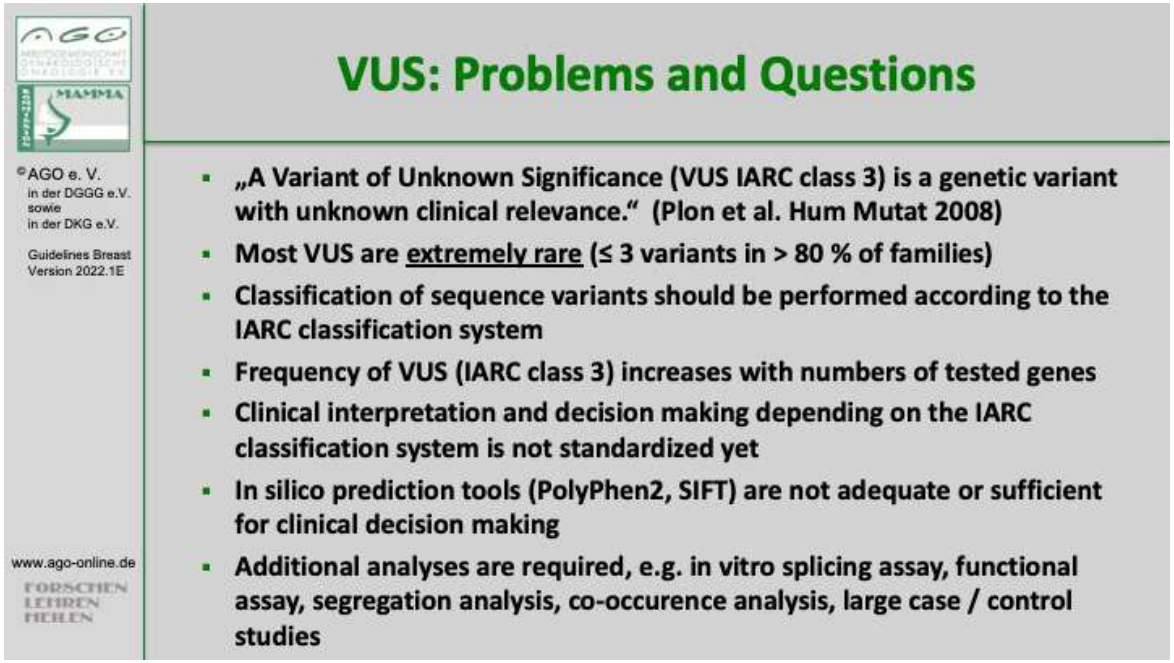

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Variant Classification Proposed by IARC

(Plon et al., Human Mutation, 2008)

Proposed Classification System for Sequence Variants Identified by Genetic Testing		
Class	**Discription**	**Probabilty of being pathogenic**
5	Definitly pathogenic	> 0.99
4	Likely pathogenic	0.95 – 0.99
3	Uncertain	0.05 – 0.949
2	Likely not pathogenic or of little clinical significance	0.001 – 0.049
1	Not pathogenic or of no clinical significance	< 0.001

Only class 4 and 5 variants are considered clinically relevant.

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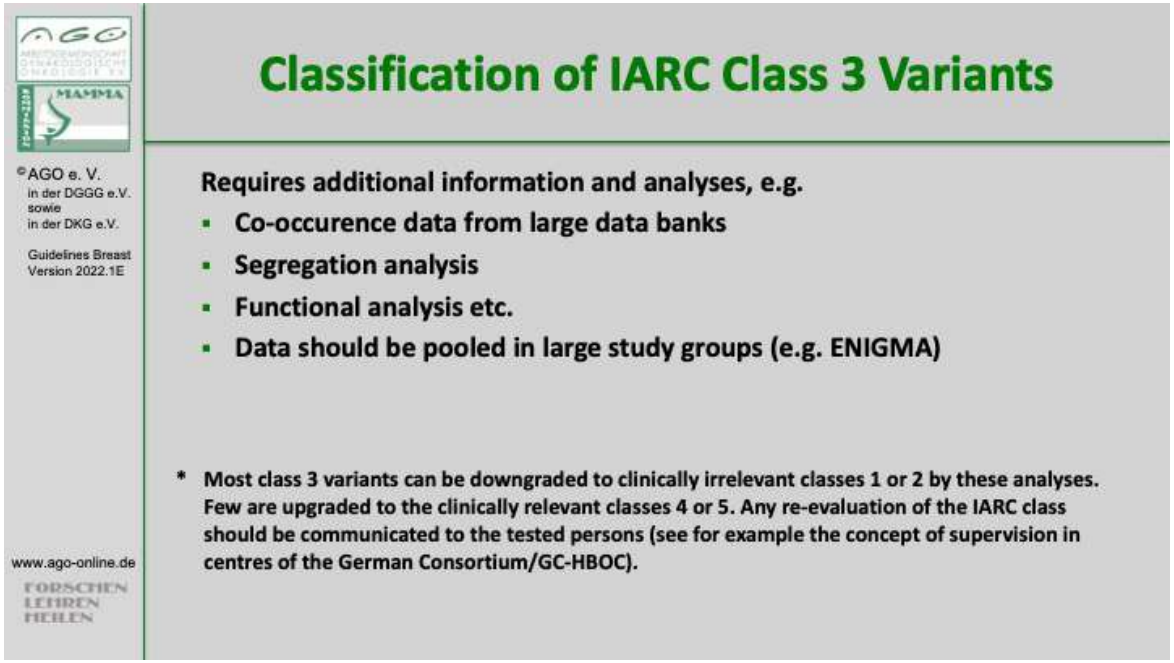

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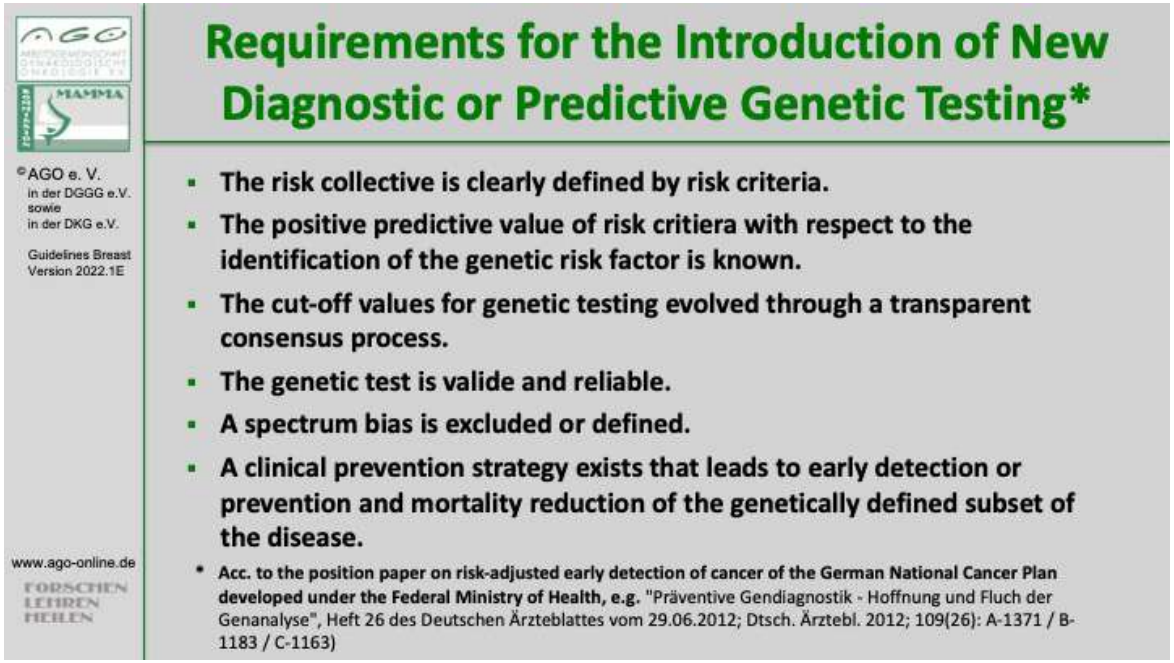

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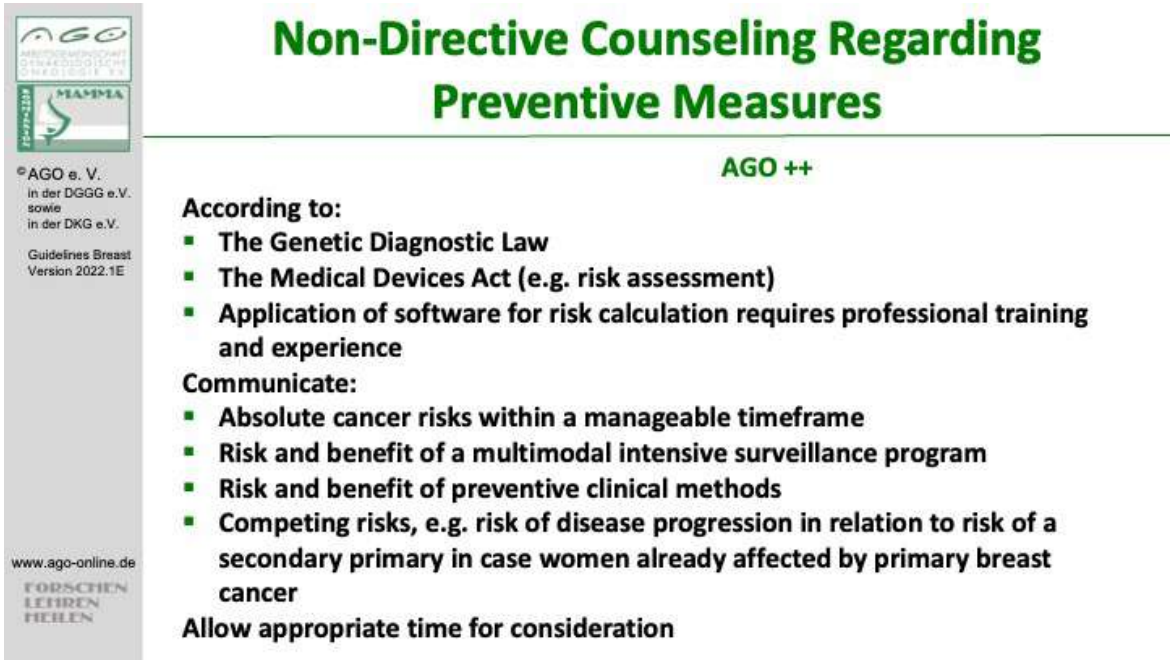

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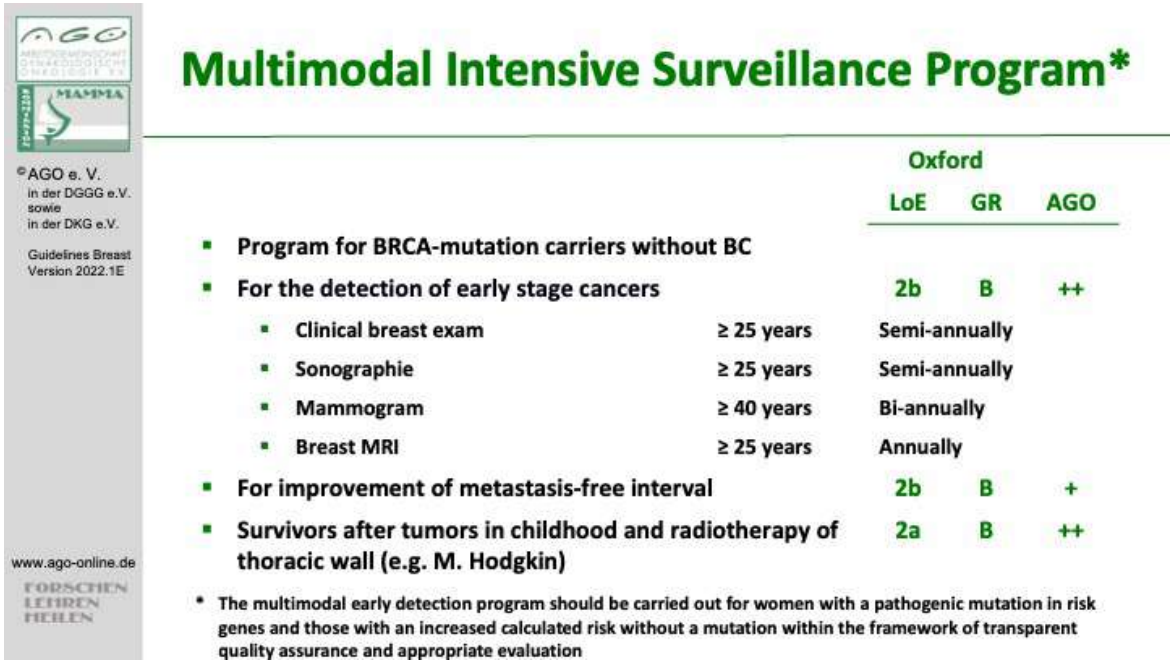

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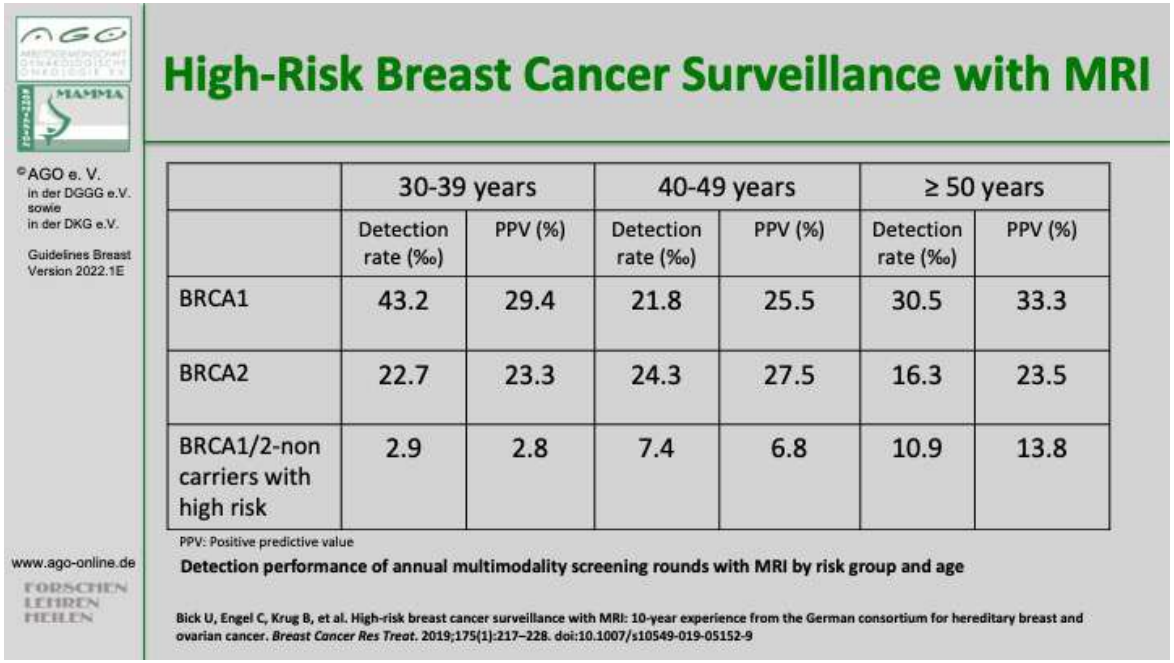

High-Risk Breast Cancer Surveillance with MRI

	30-39 years		40-49 years		≥ 50 years	
	Detection rate (‰)	PPV (%)	Detection rate (‰)	PPV (%)	Detection rate (‰)	PPV (%)
BRCA1	43.2	29.4	21.8	25.5	30.5	33.3
BRCA2	22.7	23.3	24.3	27.5	16.3	23.5
BRCA1/2-non carriers with high risk	2.9	2.8	7.4	6.8	10.9	13.8

PPV: Positive predictive value

Detection performance of annual multimodality screening rounds with MRI by risk group and age

Bick U, Engel C, Krug B, et al. High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer. *Breast Cancer Res Treat*. 2019;175(1):217–228. doi:10.1007/s10549-019-05152-9

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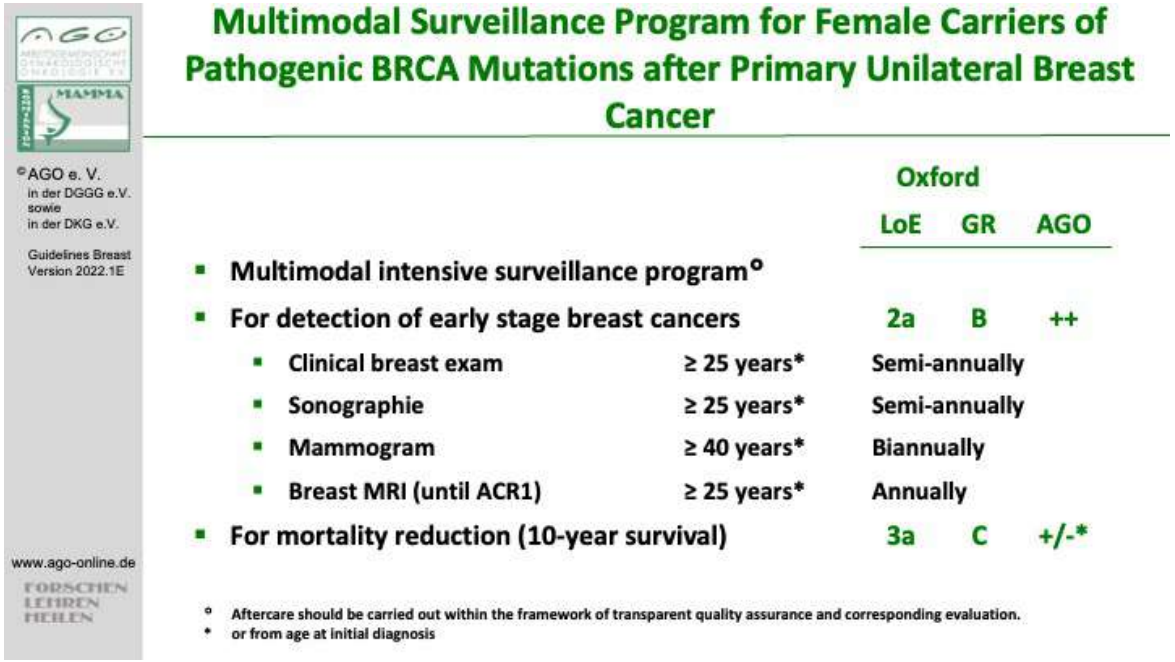

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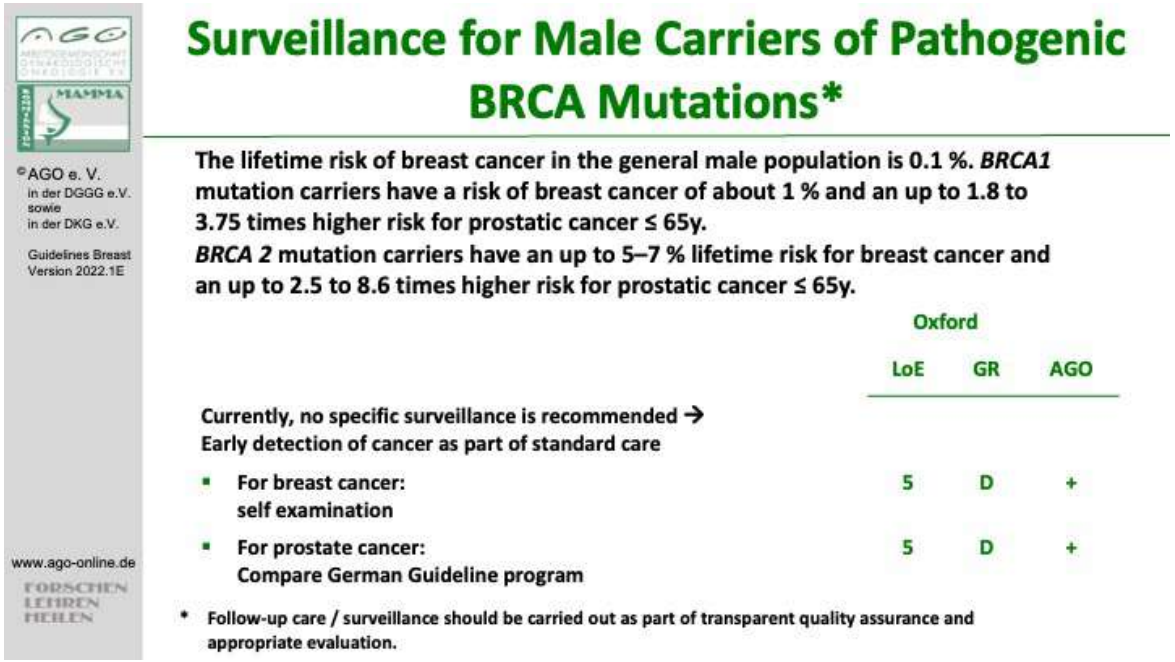

Surveillance for Male Carriers of Pathogenic BRCA Mutations*

The lifetime risk of breast cancer in the general male population is 0.1 %. *BRCA1* mutation carriers have a risk of breast cancer of about 1 % and an up to 1.8 to 3.75 times higher risk for prostatic cancer ≤ 65y.
***BRCA 2* mutation carriers have an up to 5–7 % lifetime risk for breast cancer and an up to 2.5 to 8.6 times higher risk for prostatic cancer ≤ 65y.**

	Oxford		
	LoE	GR	AGO
Currently, no specific surveillance is recommended → Early detection of cancer as part of standard care			
▪ **For breast cancer: self examination**	5	D	+
▪ **For prostate cancer: Compare German Guideline program**	5	D	+

* **Follow-up care / surveillance should be carried out as part of transparent quality assurance and appropriate evaluation.**

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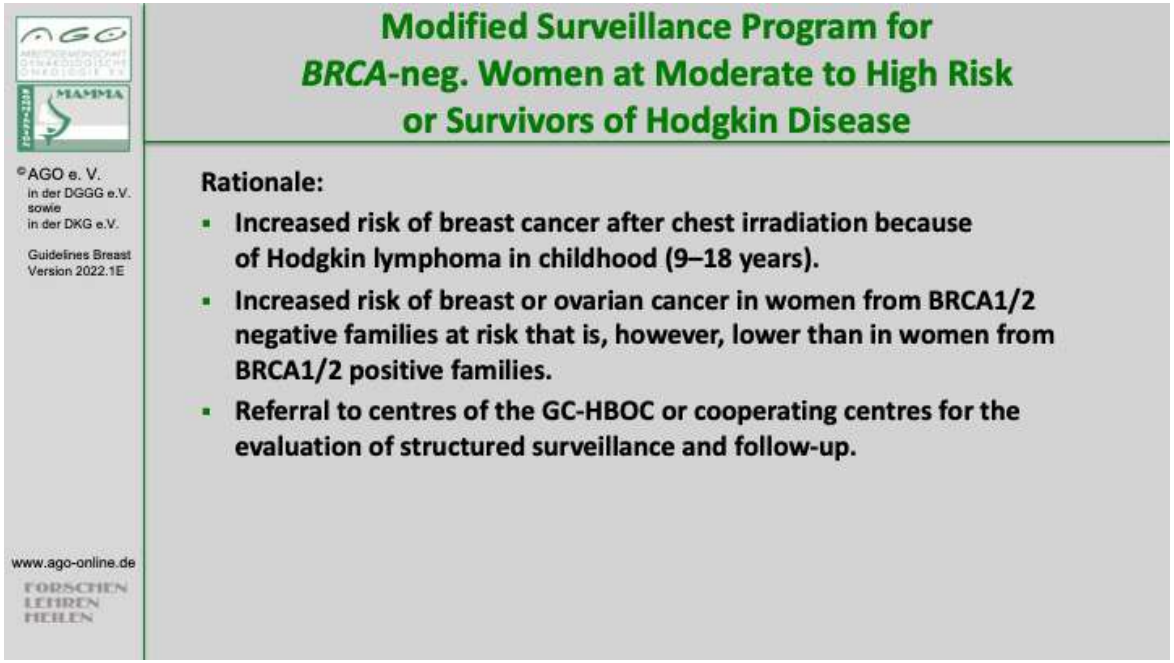

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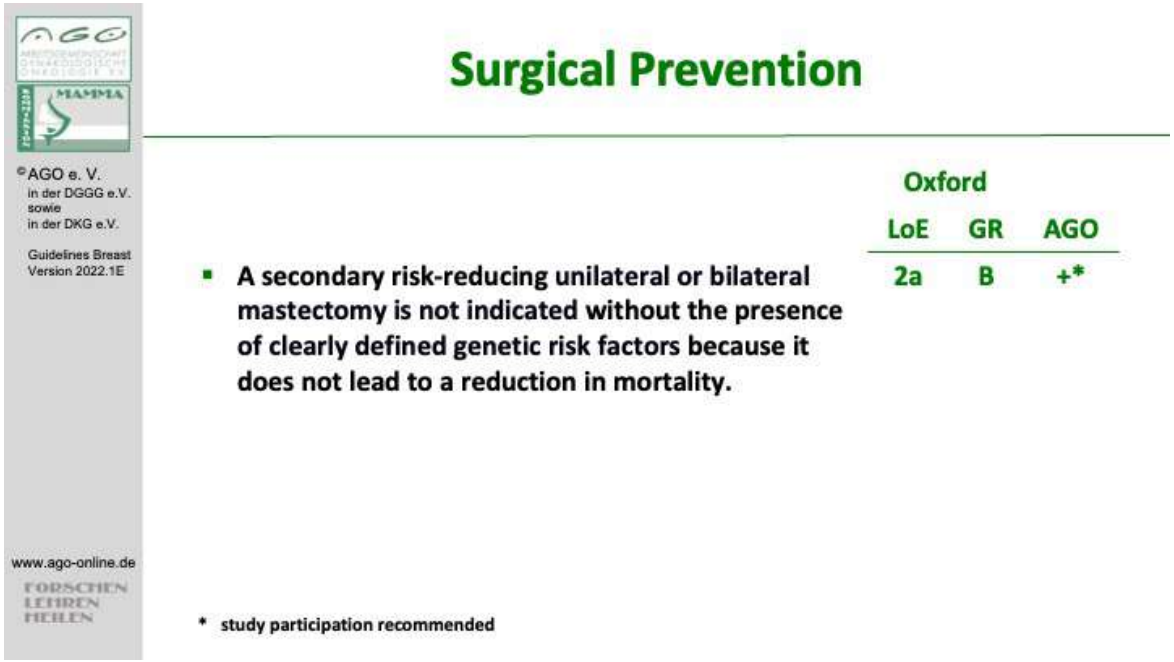

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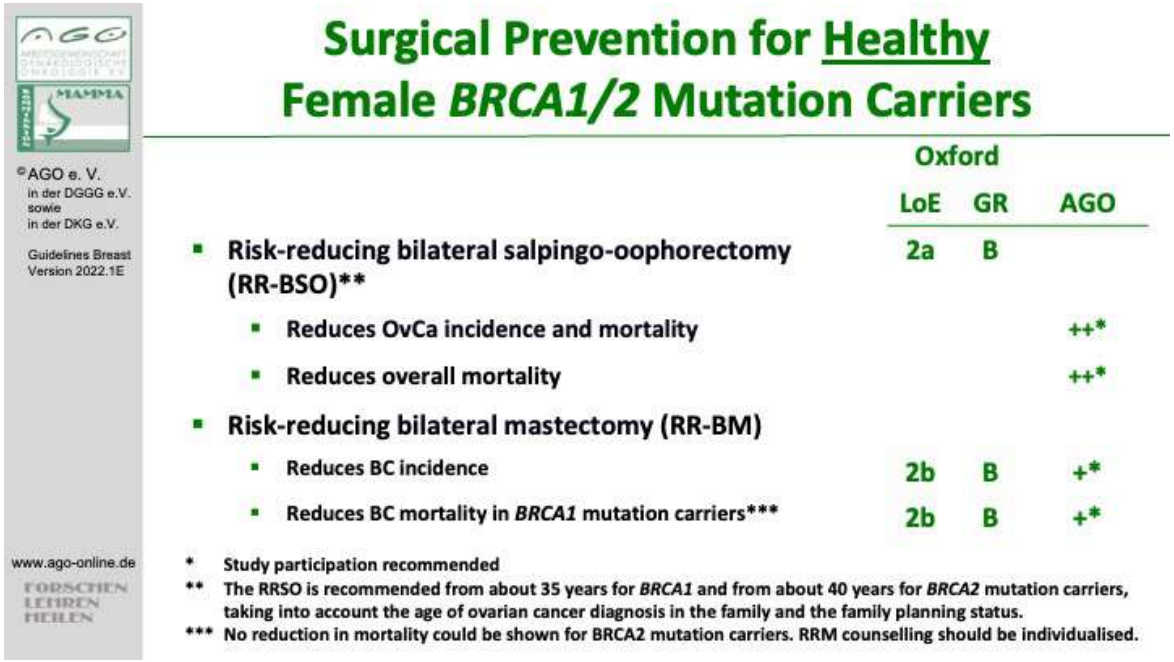

Surgical Prevention for Healthy Female *BRCA1/2* Mutation Carriers

	Oxford LoE	Oxford GR	AGO
▪ Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)**	2a	B	
▪ Reduces OvCa incidence and mortality			++*
▪ Reduces overall mortality			++*
▪ Risk-reducing bilateral mastectomy (RR-BM)			
▪ Reduces BC incidence	2b	B	+*
▪ Reduces BC mortality in *BRCA1* mutation carriers***	2b	B	+*

* Study participation recommended
** The RRSO is recommended from about 35 years for *BRCA1* and from about 40 years for *BRCA2* mutation carriers, taking into account the age of ovarian cancer diagnosis in the family and the family planning status.
*** No reduction in mortality could be shown for BRCA2 mutation carriers. RRM counselling should be individualised.

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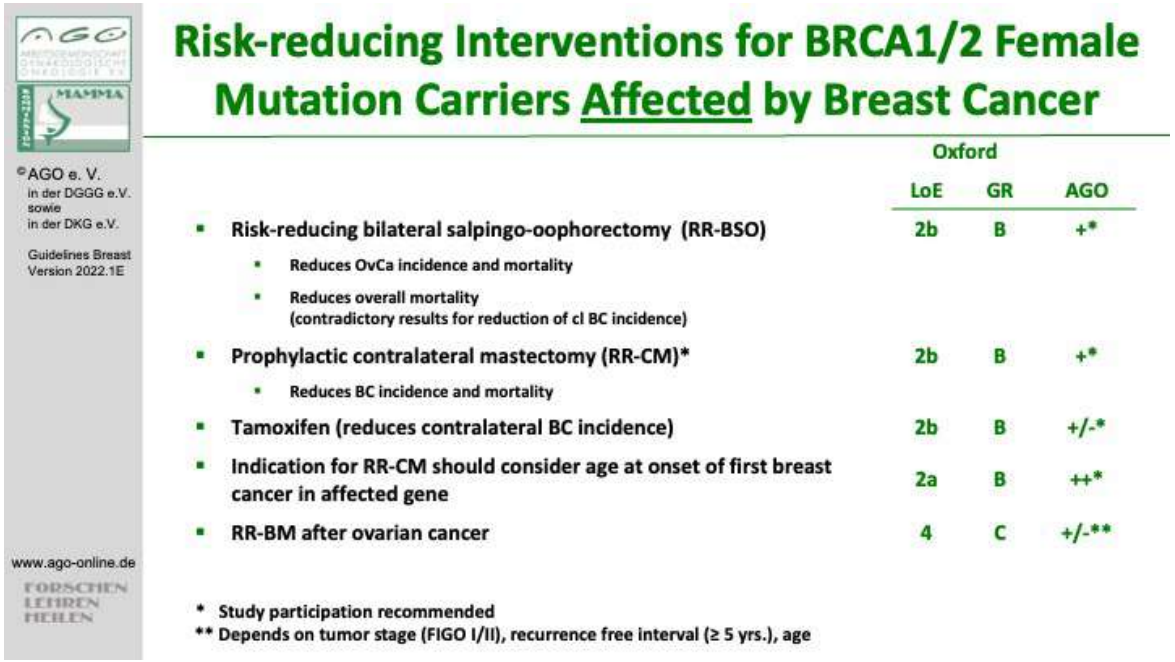

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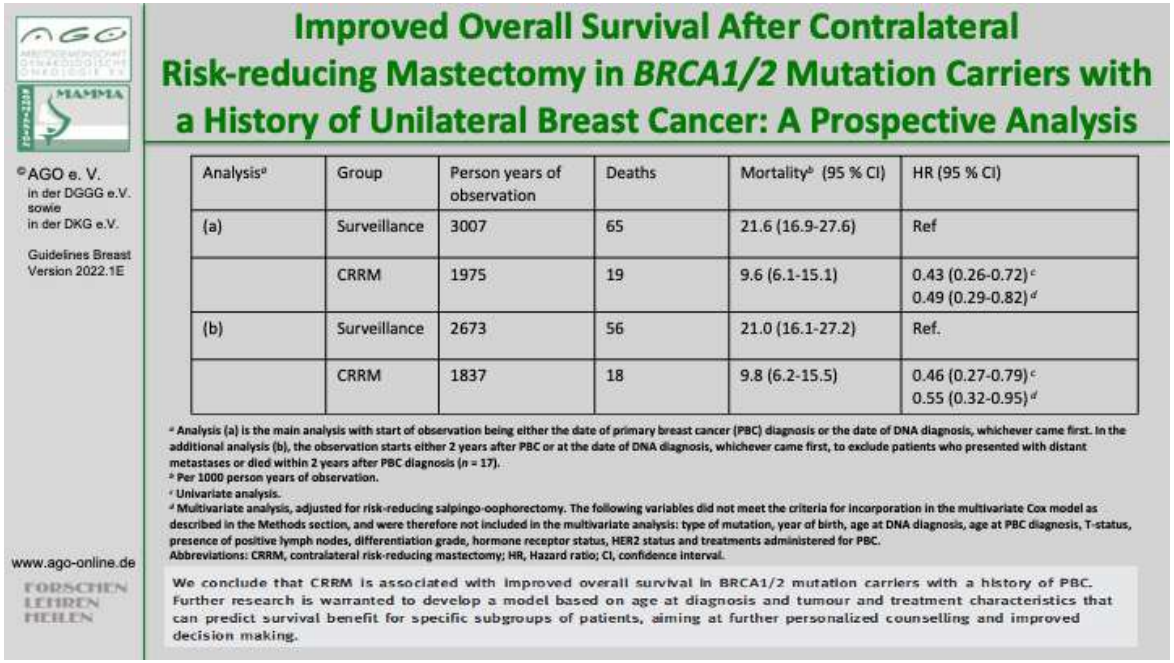

Improved Overall Survival After Contralateral Risk-reducing Mastectomy in *BRCA1/2* Mutation Carriers with a History of Unilateral Breast Cancer: A Prospective Analysis

Analysis[a]	Group	Person years of observation	Deaths	Mortality[b] (95 % CI)	HR (95 % CI)
(a)	Surveillance	3007	65	21.6 (16.9-27.6)	Ref
	CRRM	1975	19	9.6 (6.1-15.1)	0.43 (0.26-0.72)[c] 0.49 (0.29-0.82)[d]
(b)	Surveillance	2673	56	21.0 (16.1-27.2)	Ref.
	CRRM	1837	18	9.8 (6.2-15.5)	0.46 (0.27-0.79)[c] 0.55 (0.32-0.95)[d]

[a] Analysis (a) is the main analysis with start of observation being either the date of primary breast cancer (PBC) diagnosis or the date of DNA diagnosis, whichever came first. In the additional analysis (b), the observation starts either 2 years after PBC or at the date of DNA diagnosis, whichever came first, to exclude patients who presented with distant metastases or died within 2 years after PBC diagnosis ($n = 17$).
[b] Per 1000 person years of observation.
[c] Univariate analysis.
[d] Multivariate analysis, adjusted for risk-reducing salpingo-oophorectomy. The following variables did not meet the criteria for incorporation in the multivariate Cox model as described in the Methods section, and were therefore not included in the multivariate analysis: type of mutation, year of birth, age at DNA diagnosis, age at PBC diagnosis, T-status, presence of positive lymph nodes, differentiation grade, hormone receptor status, HER2 status and treatments administered for PBC.
Abbreviations: CRRM, contralateral risk-reducing mastectomy; HR, Hazard ratio; CI, confidence interval.

We conclude that CRRM is associated with improved overall survival in BRCA1/2 mutation carriers with a history of PBC. Further research is warranted to develop a model based on age at diagnosis and tumour and treatment characteristics that can predict survival benefit for specific subgroups of patients, aiming at further personalized counselling and improved decision making.

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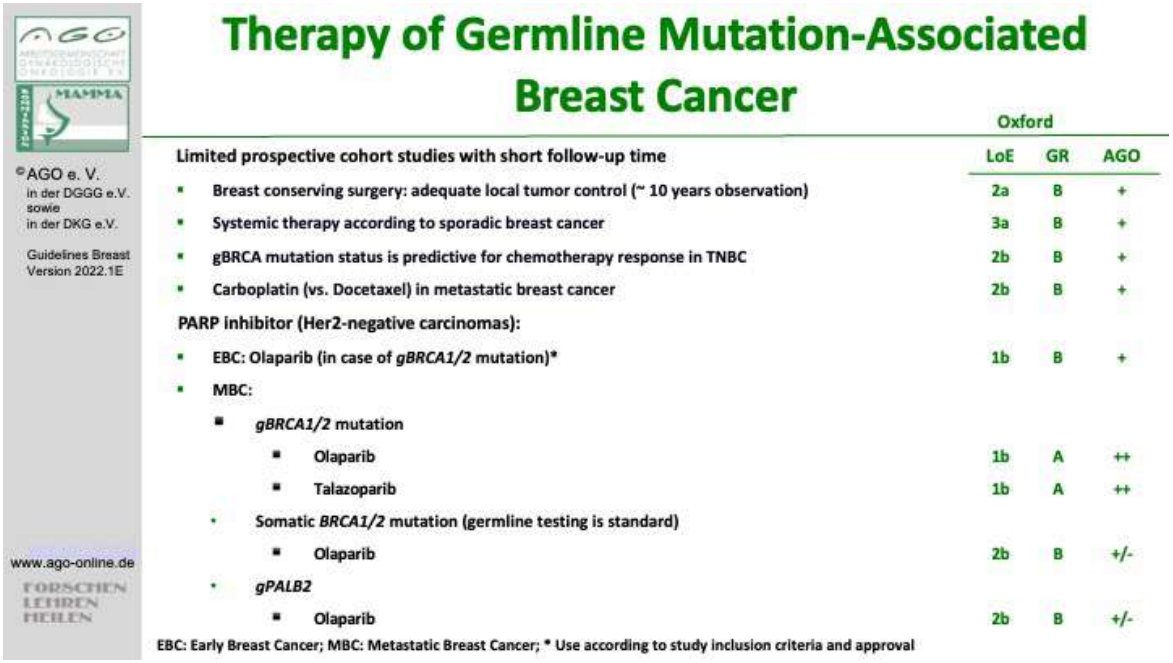

Therapy of Germline Mutation-Associated Breast Cancer

Limited prospective cohort studies with short follow-up time	Oxford LoE	GR	AGO
▪ Breast conserving surgery: adequate local tumor control (~ 10 years observation)	2a	B	+
▪ Systemic therapy according to sporadic breast cancer	3a	B	+
▪ gBRCA mutation status is predictive for chemotherapy response in TNBC	2b	B	+
▪ Carboplatin (vs. Docetaxel) in metastatic breast cancer	2b	B	+
PARP inhibitor (Her2-negative carcinomas):			
▪ EBC: Olaparib (in case of *gBRCA1/2* mutation)*	1b	B	+
▪ MBC:			
▪ *gBRCA1/2* mutation			
▪ Olaparib	1b	A	++
▪ Talazoparib	1b	A	++
▪ Somatic *BRCA1/2* mutation (germline testing is standard)			
▪ Olaparib	2b	B	+/-
▪ *gPALB2*			
▪ Olaparib	2b	B	+/-

EBC: Early Breast Cancer; MBC: Metastatic Breast Cancer; * Use according to study inclusion criteria and approval

BCS bei BRCA 1/2 Mutationsträgern

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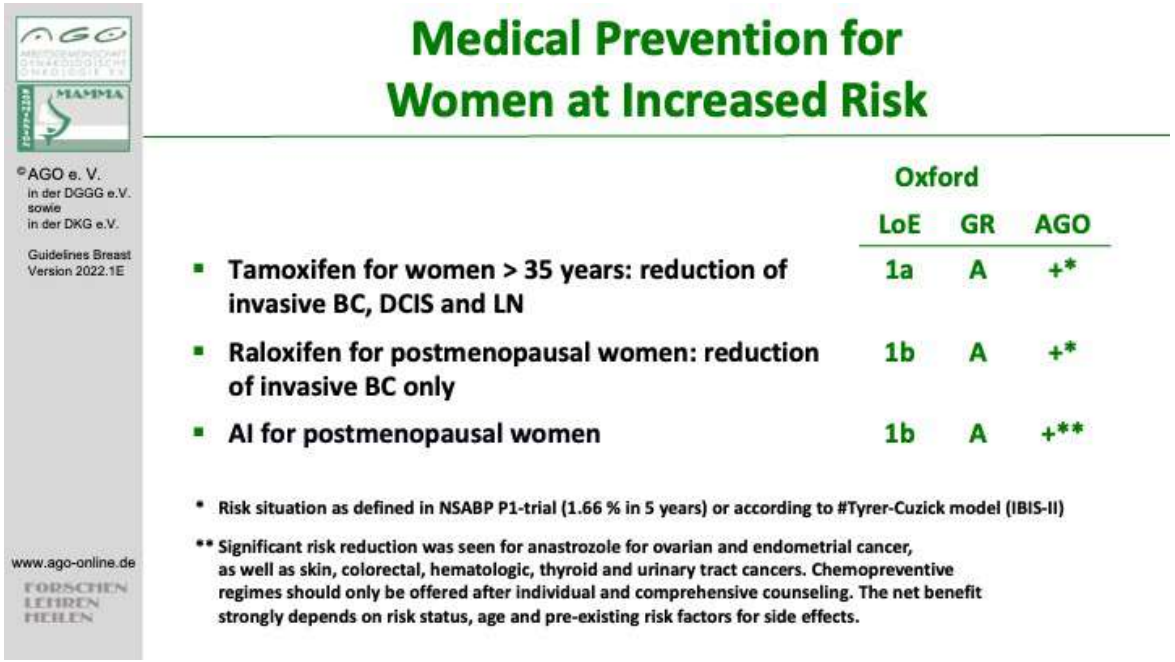

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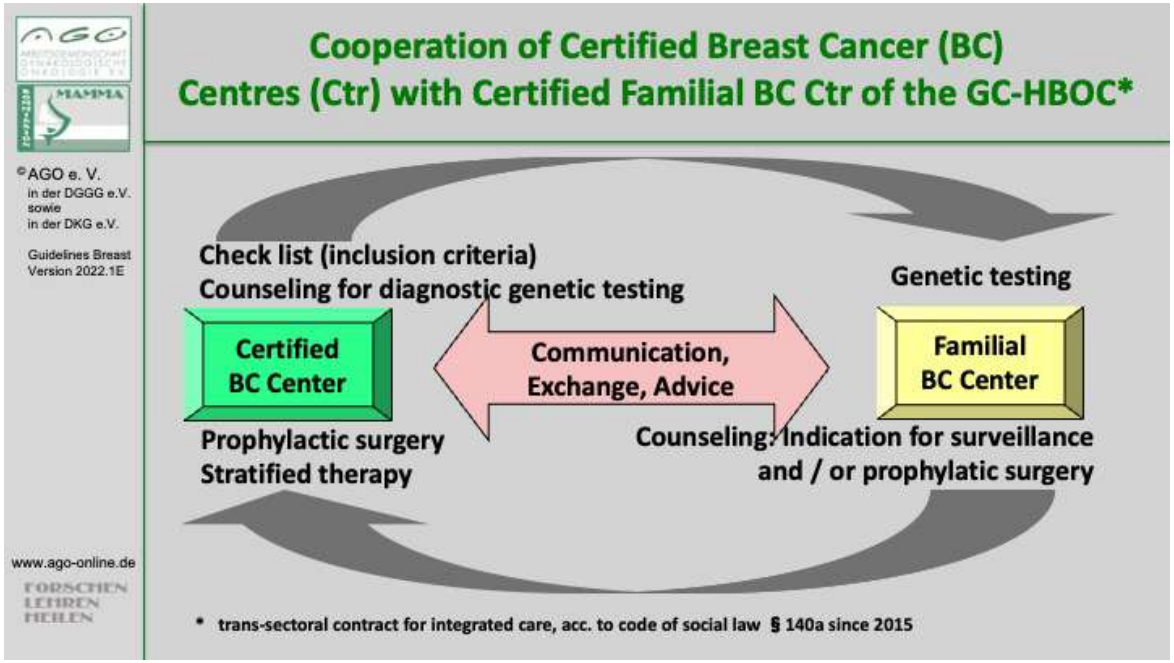
Cooperation of Certified Breast Cancer (BC) Centres (Ctr) with Certified Familial BC Ctr of the GC-HBOC*
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