Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2023.1E

FORSCHEN
LEHREN
HEILEN

Breast Cancer Risk, Genetics and Prevention

Guidelines Breast
Version 2023.1E

Breast Cancer Risk and Prevention

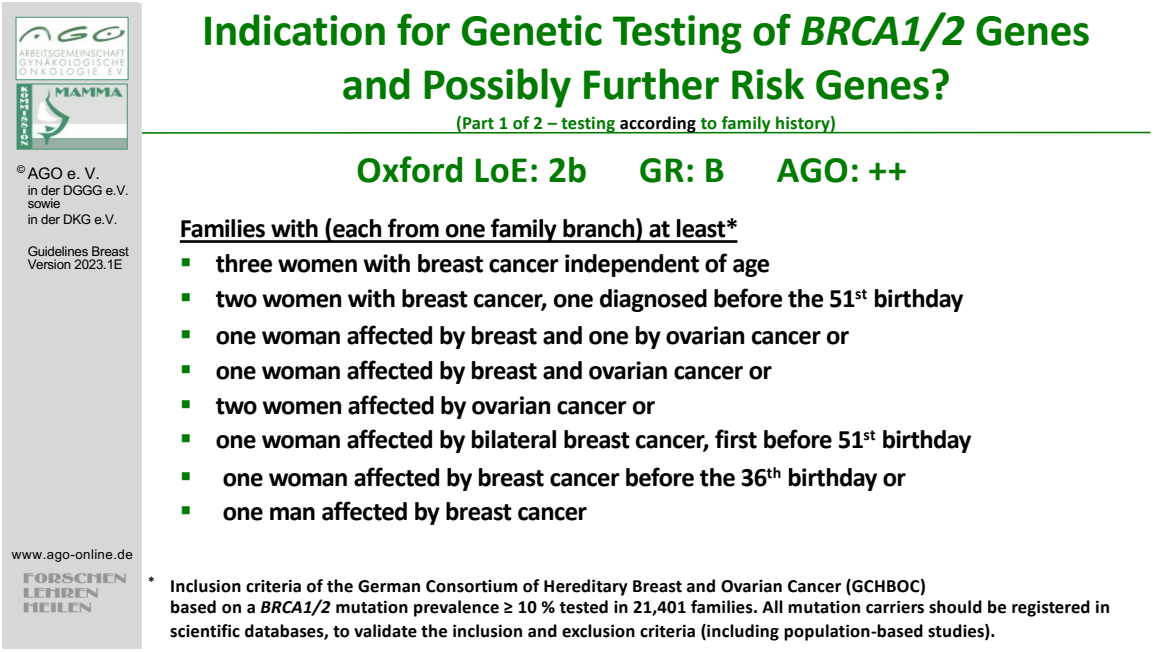
- **Versions 2003–2022:**
  Albert / Bischoff / Blohmer / Dall / Ditsch / Fasching / Fehm / Gerber / Kiechle / Maass / Müller-Schimpfle / Mundhenke / Park-Simon / Rhiem / Rody / Schmidt / Schmutzler / Stickeler / Thomssen / Witzel

- **Version 2023:**
  Schütz / Thomssen

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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3. Meindl A, German Consortium for Hereditary B, Ovarian C. Comprehensive analysis of 989 patients with breast or ovarian cancer provides BRCA1 and BRCA2 mutation profiles and frequencies for the German population. Int J Cancer. 2002;97(4):472-80.
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Indication for Genetic Testing of *BRCA1/2* Genes and Possibly Further Risk Genes?

(Part 2 of 2 - testing according to disease)

Oxford LoE: 2b GR: B AGO: ++

- **Other recommended criteria:**
  - **own disease of triple negative breast cancer diagnosed before 60th birthday**
  - **own disease of ovarian cancer before 80th birthday**
  - **if therapeutically relevant (e.g. PARPi; BRCA1 and BRCA2 only; possibly PALB2)**

1. Couch FJ, Hart SN, Sharma P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. J Clin Oncol. 2015;33(4):304-11.
2. Engel C, Rhiem K, Hahnen E, et al. Prevalence of pathogenic BRCA1/2 germline mutations among 802 women with unilateral triple-negative breast cancer without family cancer history. *BMC Cancer*. 2018;18(1):265. Published 2018 Mar 7. doi:10.1186/s12885-018-4029-y
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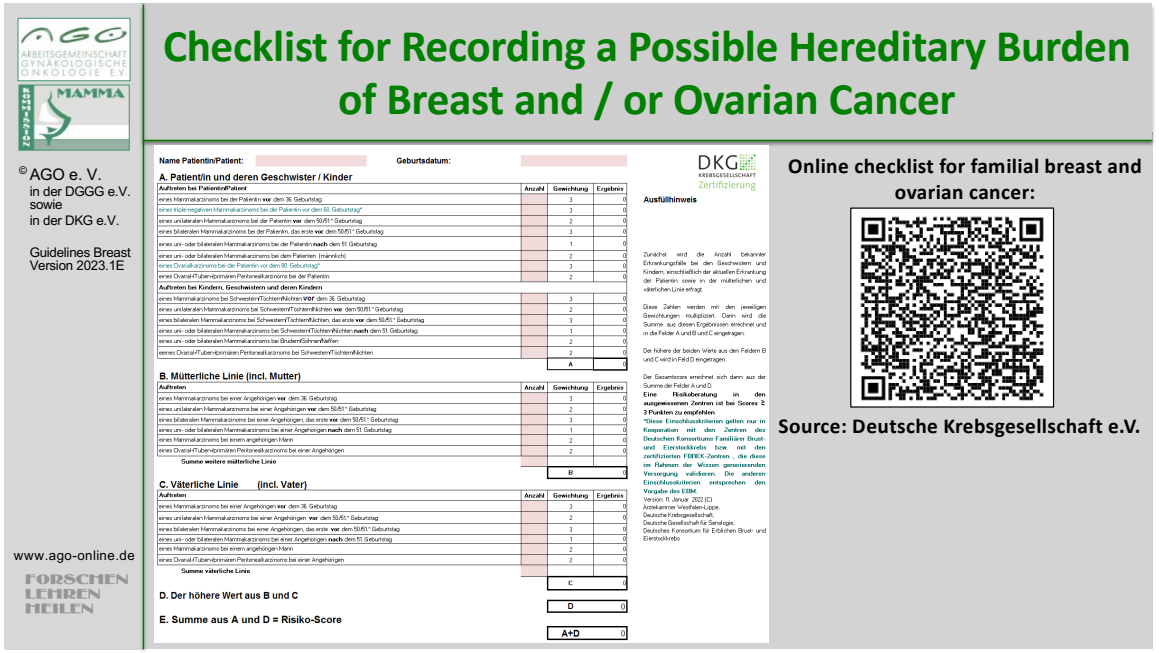

Hier ist das Online Tool zur Checkliste „Familiärer Brust- und Eierstockkrebs“ hinterlegt:
https://www.krebsgesellschaft.de/zertdokumente.html?file=files/dkg/deutsche-krebsgesellschaft/content/pdf/Zertifizierung/Checklisten-und-Algorithmen/checkliste_erbliche_belastung_brust_gyn-220118.xlsx&cid=98969

Referenzen:

1. Kast K, Rhiem K, Wappenschmidt B, et al., Prevalence of BRCA1/2 germline mutations in 21.401 families with breast and ovarian cancer. J Med Genet 2016;53:465-71.
2. Rhiem K, Bücker-Nott HJ, Hellmich M, et al. Benchmarking of a checklist for the identification of familial risk for breast and ovarian cancers in a prospective cohort. Breast J. 2019;25(3):455–460. doi:10.1111/tbj.13257

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1. Kast K, Rhiem K, Wappenschmidt B, et al., Prevalence of BRCA1/2 germline mutations in 21.401 families with breast and ovarian cancer. J Med Genet 2016;53:465-71.
2. Rhiem K, Bücker-Nott HJ, Hellmich M, et al. Benchmarking of a checklist for the identification of familial risk for breast and ovarian cancers in a prospective cohort. Breast J. 2019;25(3):455–460. doi:10.1111/tbj.13257

Risk estimation for syndrome-associated breast cancer (non-BRCA)

	Oxford		
	LoE	GR	AGO
History and family history over at least three generation (including age of first disease)	2b	B	++

- **Characteristic disease**
  - **Breast and ovarian cancer**
- **Further disease**
  - **Pancreatic, thyroid, colorectal, stomache, hepatobilear, urogenital, lung cancer, melanoma, osteosarcoma, leukemia, lymphoma**
  - **Kidney cancer**
  - **Testinal cancer**
  - **Endometrial cancer**
  - **Prostate cancer**

1. Antoniou AC, Casadei S, Heikkinen T, et al. Breast-cancer risk in families with mutations in PALB2. N Engl J Med. 2014;371(6):497-506.
2. Benusiglio PR, Malka D, Rouleau E, et al. CDH1 germline mutations and the hereditary diffuse gastric and lobular breast cancer syndrome: a multicentre study. J Med Genet. 2013;50(7):486-9
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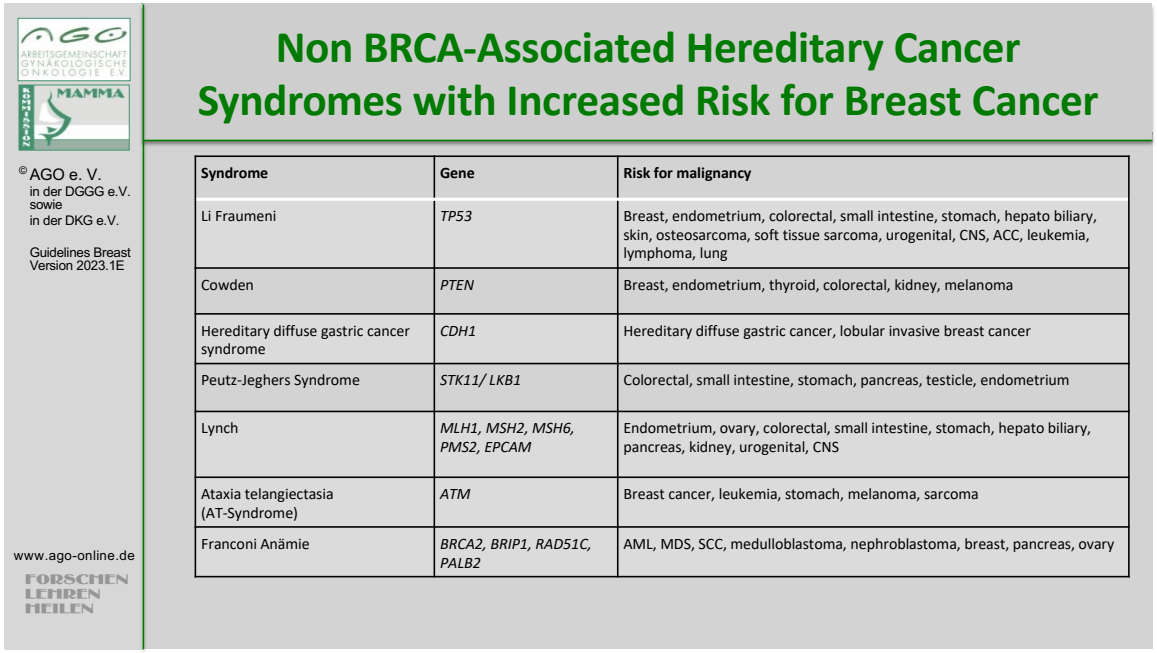
14. Weber-Lassalle N, Hauke J, Ramser J, et al. BRIP1 loss-of-function mutations confer high risk for familial ovarian cancer, but not familial breast cancer. Breast Cancer Res. 2018 Jan 24;20(1):7. doi: 10.1186/s13058-018-0935-9.



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 biliary, 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

1. Antoniou AC, Casadei S, Heikkinen T, et al. Breast-cancer risk in families with mutations in PALB2. N Engl J Med. 2014;371(6):497-506.
2. Benusiglio PR, Malka D, Rouleau E, et al. CDH1 germline mutations and the hereditary diffuse gastric and lobular breast cancer syndrome: a multicentre study. J Med Genet. 2013;50(7):486-9
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11. Meindl A, Hellebrand H, Wiek C, et al. Germline mutations in breast and ovarian cancer pedigrees establish RAD51C as a human cancer susceptibility gene. Nat Genet. 2010;42(5):410-4.
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14. Weber-Lassalle N, Hauke J, Ramser J, et al. BRIP1 loss-of-function mutations confer high risk for familial ovarian cancer, but not familial breast cancer. Breast Cancer Res. 2018 Jan 24;20(1):7. doi: 10.1186/s13058-018-0935-9

Non-Directive Counseling Regarding Preventive Measures

AGO ++

According to:

- **The Genetic Diagnostic Law**
- **The Medical Devices Act (e.g. risk assessment)**
- **Application of software for risk calculation requires professional training and experience**

Communicate:

- **Absolute cancer risks within a manageable timeframe**
- **Risk and benefit of a multimodal intensive surveillance program**
- **Risk and benefit of preventive clinical methods**
- **Competing risks, e.g. risk of disease progression in relation to risk of a secondary primary in case women already affected by primary breast cancer**

Allow appropriate time for consideration

1. Phi XA, Houssami N, Hooning MJ et al., Accuracy of screening women at familial risk of breast cancer without a known gene mutation.. Eur J of Cancer 2017;85:31-38

SOFTWARE (BOADICEA, IBIS)

1. Lee A, Mavaddat N, Wilcox AN et al. BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors. Genet Med. 2019 Aug;21(8):1708-1718. Erratum in: Genet Med. 2019 Feb 21;:

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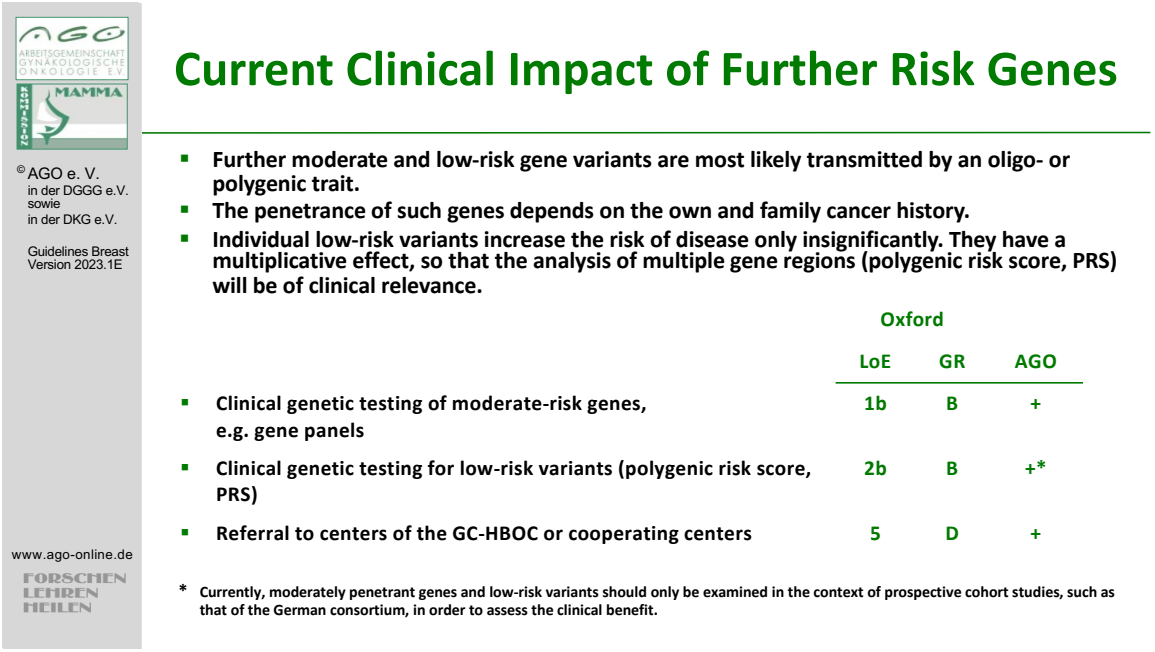

Analyse von moderaten Risikogenen e.g. Genpanel

1. Borde J, Ernst C, Wappenschmidt B et al. Performance of breast cancer polygenic risk scores in 760 female CHEK2 germline mutation carriers. J Natl Cancer Inst. 2020 Dec 29:djaa203. doi: 10.1093/jnci/djaa203. Epub ahead of print. PMID: 33372680.
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9. Michailidou K, Beesley J, Lindstrom S, et al. Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. Nat Genet. 2015;47(4):373-80.
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Analyse von Niedrigrisikovarianten (Polygenic risk score, PRS)

1. Jiao Y, Truong T, Eon-Marchais S, et al. Association and performance of polygenic risk scores for breast cancer among French women presenting or not a familial predisposition to the disease. Eur J Cancer. 2023 Jan;179:76-86.
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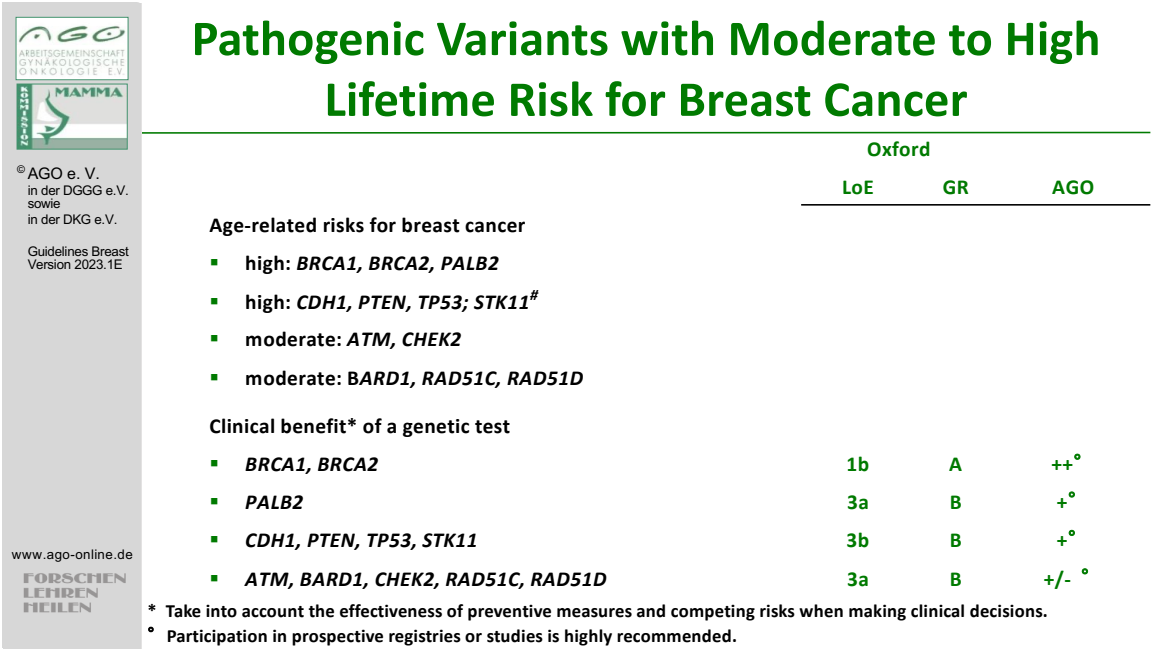

Pathogenic Variants with Moderate to High Lifetime Risk for Breast Cancer

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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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CDH1:

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PTEN:

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TP53:

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Klinischer Nutzen:

1. Couch FJ, Nathanson KL, Offit K. Two decades after BRCA: setting paradigms in personalized cancer care and prevention. Science. 2014;343(6178):1466-70.
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familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet. 2005;365(9473):1769-78.

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State of research: Relevance of Genetic and non-Genetic Risk Factors

Guidelines Breast
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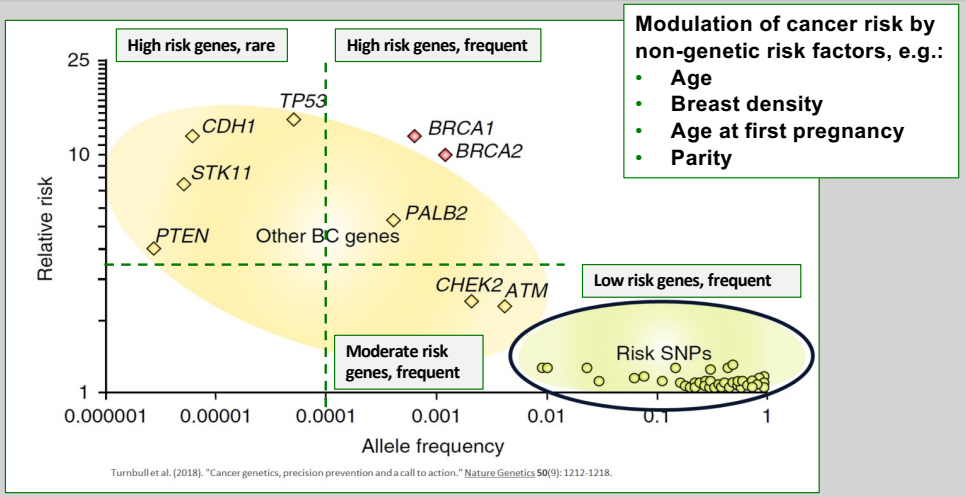

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Estimated Cumulative Risk of Breast Cancer with Protein-Truncating Variants in 8 Genes

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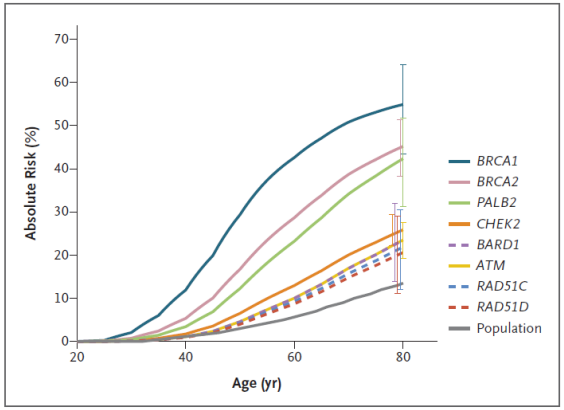

Shown are cumulative risks of breast cancer through 80 years of age for protein-truncating variants in 8 genes that had significant evidence of an association with breast cancer overall, on the basis of estimated odds ratios from population-based studies. Baseline absolute risks were derived from population incidences in the United Kingdom in 2016. The I bars indicate 95 % confidence intervals.

Dorling L, Carvalho S, Allen J et al. Breast-Cancer Risk Genes — Association Analysis in More than 113,000 Women. January 20, 2021 DOI: 10.1056/NEJMoa1913948

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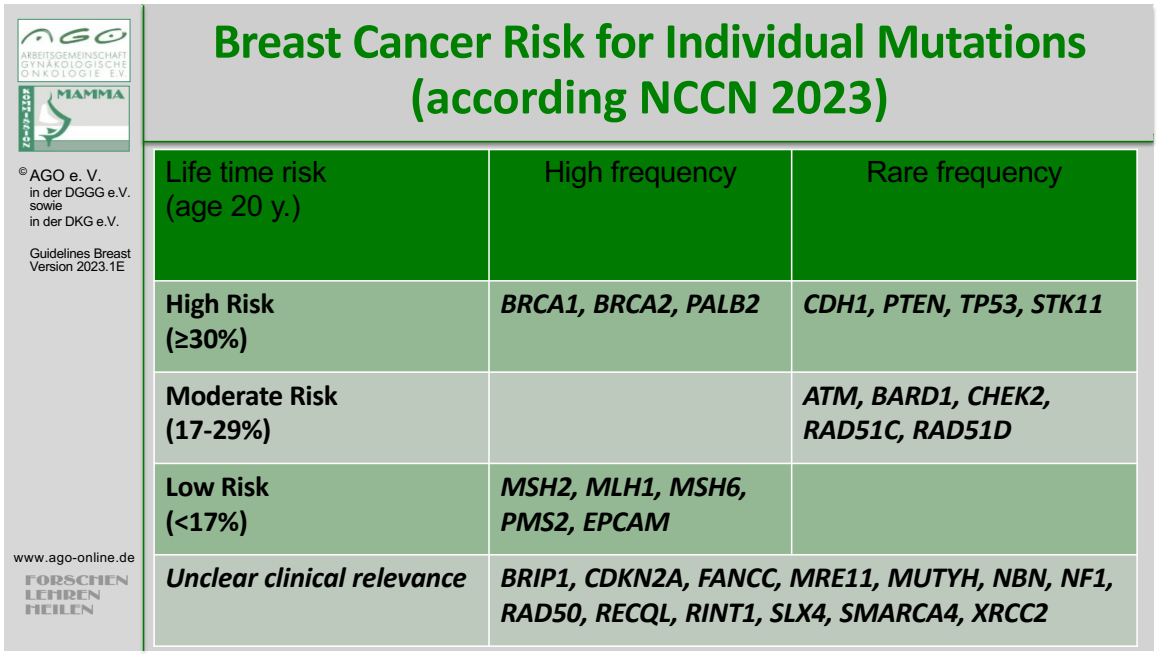

Life time risk (age 20 y.)	High frequency	Rare frequency
High Risk (≥30%)	***BRCA1, BRCA2, PALB2***	***CDH1, PTEN, TP53, STK11***
Moderate Risk (17-29%)		***ATM, BARD1, CHEK2, RAD51C, RAD51D***
Low Risk (<17%)	***MSH2, MLH1, MSH6, PMS2, EPCAM***	
Unclear clinical relevance	***BRIP1, CDKN2A, FANCC, MRE11, MUTYH, NBN, NF1, RAD50, RECQL, RINT1, SLX4, SMARCA4, XRCC2***	

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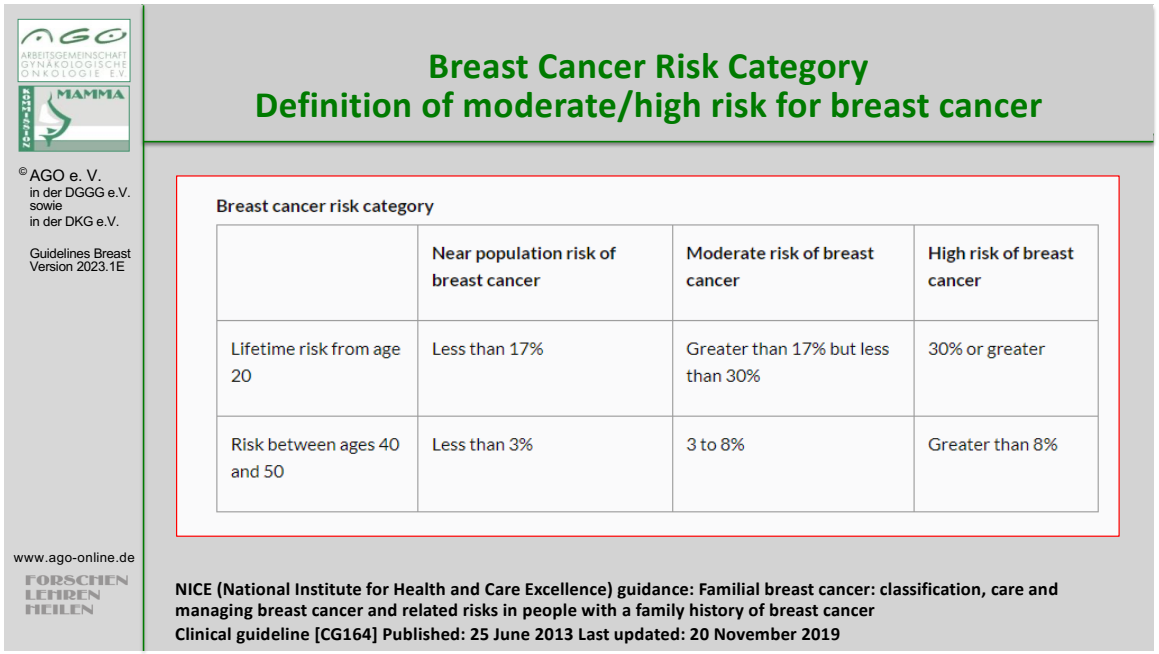

Breast Cancer Risk Category
Definition of moderate/high risk for breast cancer

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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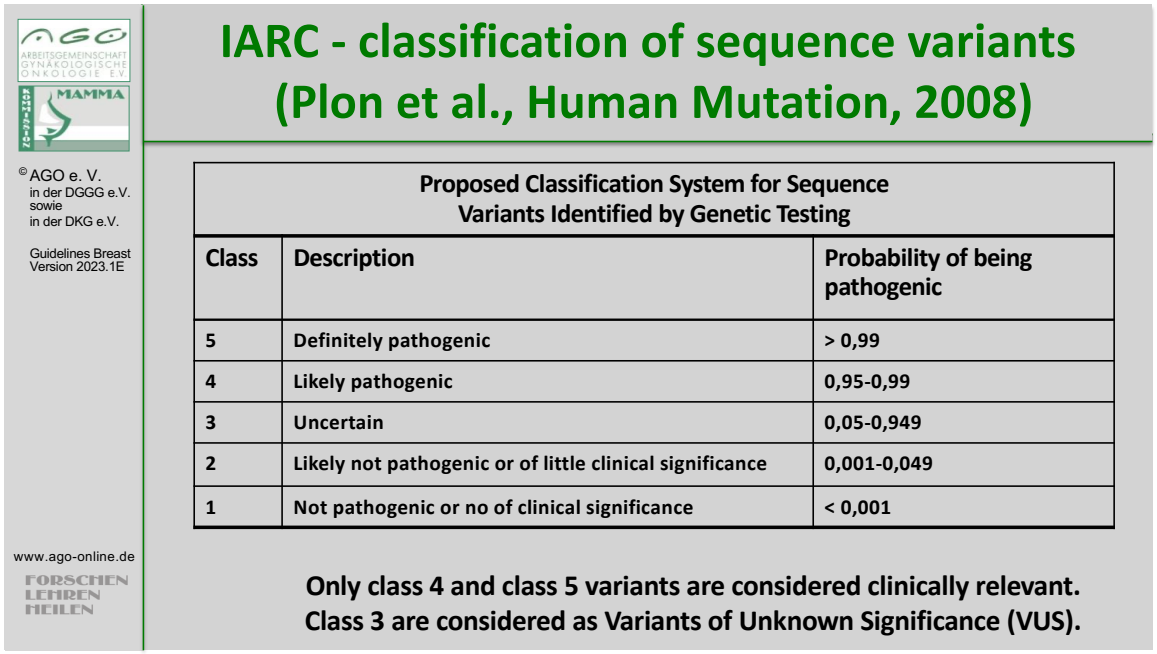

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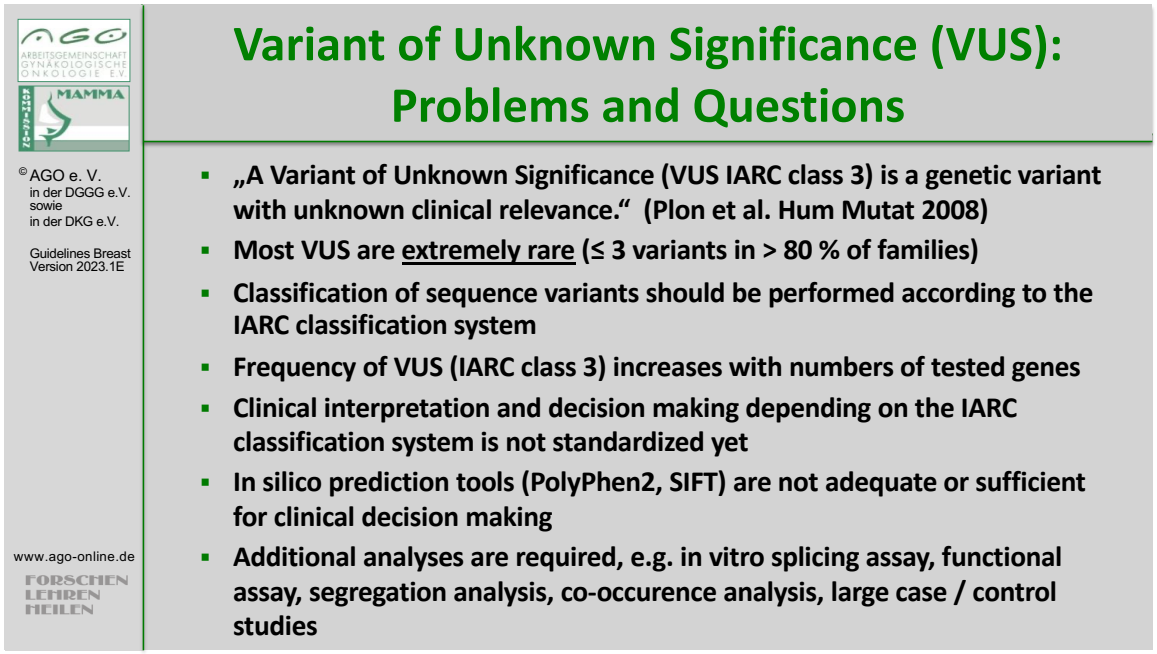

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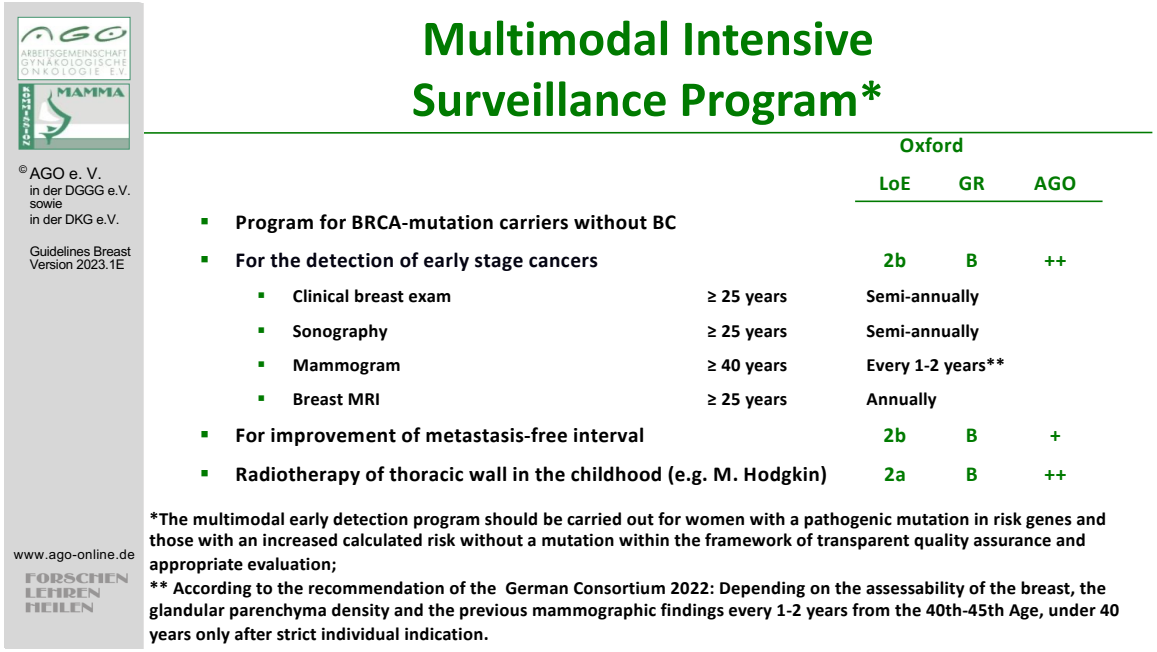

Multimodal Intensive Surveillance Program*

		Oxford LoE	GR	AGO
▪ Program for BRCA-mutation carriers without BC				
▪ For the detection of early stage cancers		2b	B	++
▪ Clinical breast exam	≥ 25 years	Semi-annually		
▪ Sonography	≥ 25 years	Semi-annually		
▪ Mammogram	≥ 40 years	Every 1-2 years**		
▪ Breast MRI	≥ 25 years	Annually		
▪ For improvement of metastasis-free interval		2b	B	+
▪ Radiotherapy of thoracic wall in the childhood (e.g. M. Hodgkin)		2a	B	++

*The multimodal early detection program should be carried out for women with a pathogenic mutation in risk genes and those with an increased calculated risk without a mutation within the framework of transparent quality assurance and appropriate evaluation;
** According to the recommendation of the German Consortium 2022: Depending on the assessability of the breast, the glandular parenchyma density and the previous mammographic findings every 1-2 years from the 40th-45th Age, under 40 years only after strict individual indication.

1. E-Learning DKG/FBREK, 2022
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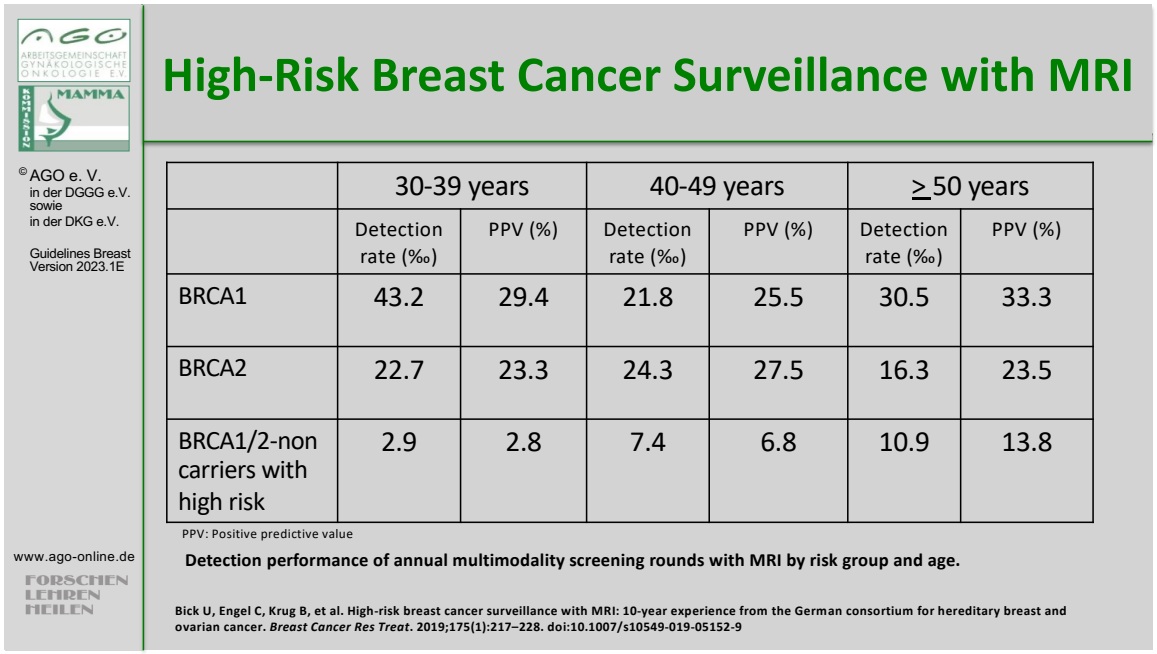

	30-39 years		40-49 years		≥ 50 years	
	Detection rate (‰)	PPV (%)	Detection rate (‰)	PPV (%)	Detection rate (‰)	PPV (%)
BRCA1	43.2	29.4	21.8	25.5	30.5	33.3
BRCA2	22.7	23.3	24.3	27.5	16.3	23.5
BRCA1/2-non carriers with high risk	2.9	2.8	7.4	6.8	10.9	13.8

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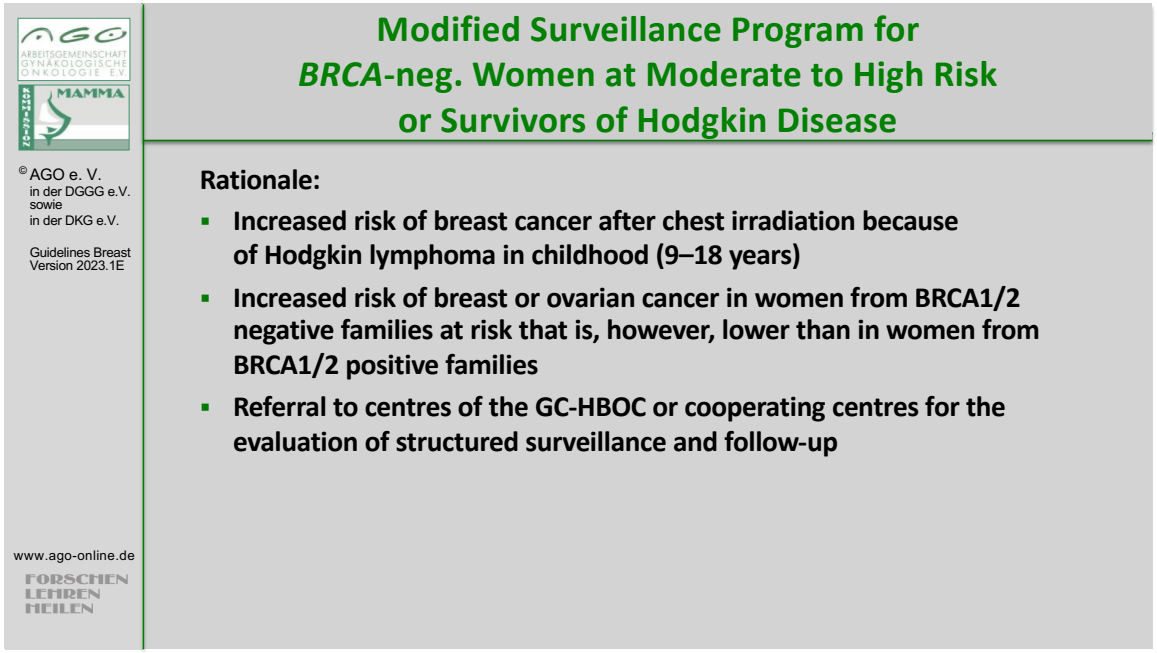

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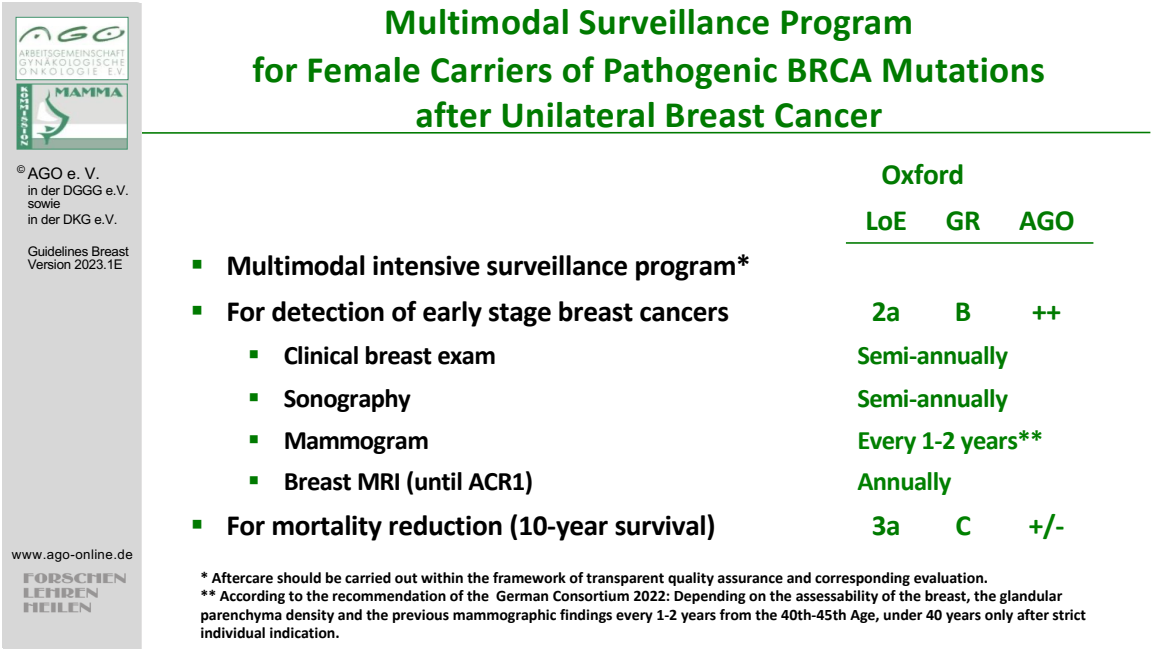

Multimodal Surveillance Program for Female Carriers of Pathogenic BRCA Mutations after Unilateral Breast Cancer

	Oxford LoE	GR	AGO
▪ **Multimodal intensive surveillance program***			
▪ **For detection of early stage breast cancers**	2a	B	++
▪ **Clinical breast exam**	Semi-annually		
▪ **Sonography**	Semi-annually		
▪ **Mammogram**	Every 1-2 years**		
▪ **Breast MRI (until ACR1)**	Annually		
▪ **For mortality reduction (10-year survival)**	3a	C	+/-

*** Aftercare should be carried out within the framework of transparent quality assurance and corresponding evaluation.**
**** According to the recommendation of the German Consortium 2022: Depending on the assessability of the breast, the glandular parenchyma density and the previous mammographic findings every 1-2 years from the 40th-45th Age, under 40 years only after strict individual indication.**

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Surveillance for Male Carriers of Pathogenic BRCA Mutations*

	Oxford		
	LoE	GR	AGO
Currently, no specific surveillance is recommended → Early detection of cancer as part of standard care			
▪ **BRCA1/2 mutation carrier: explanation of risks for cancer disease including male family members**	5	D	++
▪ **For breast cancer: self examination**	5	D	+
▪ **For prostate cancer: Compare German Guideline program**	5	D	+

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.

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

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Surgical Prevention

	Oxford		
	LoE	GR	AGO
▪ **Risk-reducing unilateral or bilateral mastectomy (RRME) without the presence of clearly defined genetic risk factors**	2a	B	-*
▪ **Axillary dissection or Sentinel lymph node excision during RRME**	2a	B	--

* **study participation recommended**

RRME ohne gentisches Risiko

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Sentinel-Lymphknoten Exzision bei RRME

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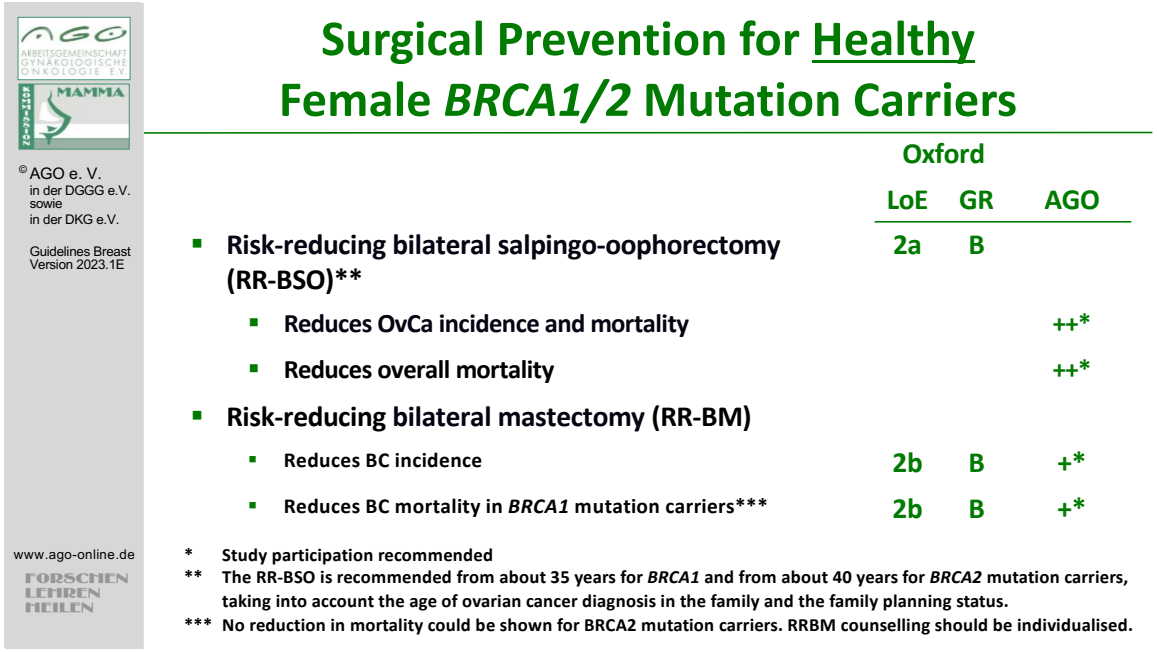

Surgical Prevention for Healthy Female *BRCA1/2* Mutation Carriers

	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 RR-BSO 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. RRBM counselling should be individualised.**

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2. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. 2010;304(9):967-75.
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5. Hoogerbrugge N, Bult P, Bonenkamp JJ, et al. Numerous high-risk epithelial lesions in familial breast cancer. Eur J Cancer. 2006;42(15):2492-8.
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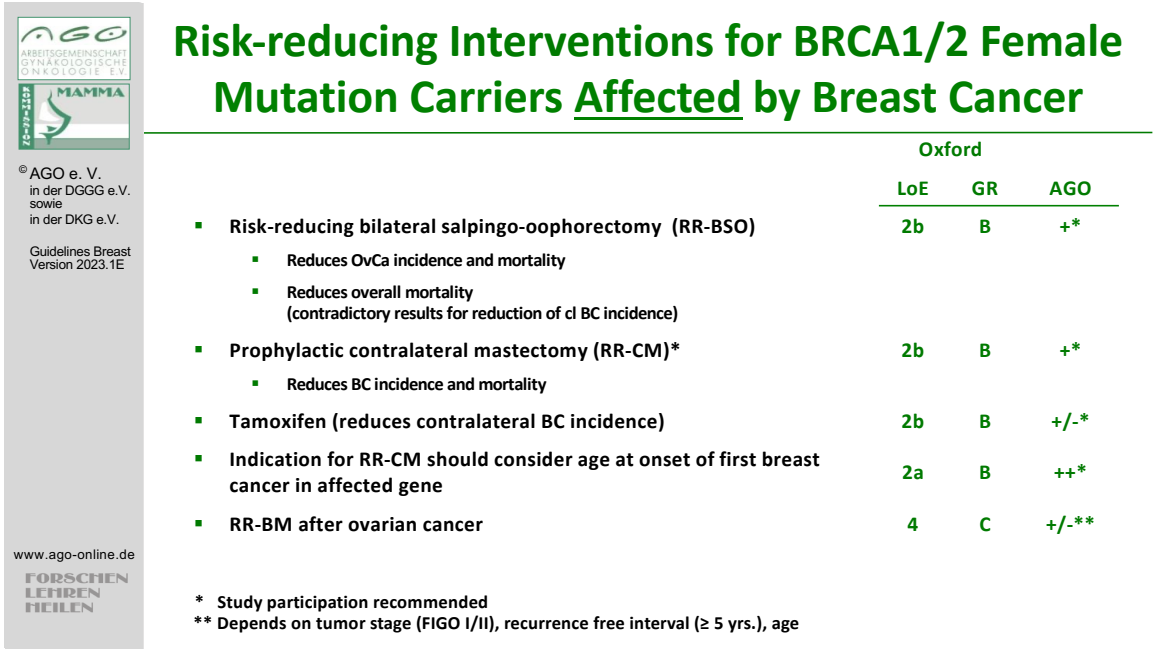

Risk-reducing Interventions for BRCA1/2 Female Mutation Carriers Affected by Breast Cancer

	Oxford		
	LoE	GR	AGO
▪ Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)	2b	B	+*
▪ Reduces OvCa incidence and mortality			
▪ Reduces overall mortality (contradictory results for reduction of cl BC incidence)			
▪ Prophylactic contralateral mastectomy (RR-CM)*	2b	B	+*
▪ Reduces BC incidence and mortality			
▪ Tamoxifen (reduces contralateral BC incidence)	2b	B	+/-*
▪ Indication for RR-CM should consider age at onset of first breast cancer in affected gene	2a	B	++*
▪ RR-BM after ovarian cancer	4	C	+/-**

* Study participation recommended
** Depends on tumor stage (FIGO I/II), recurrence free interval (≥ 5 yrs.), age

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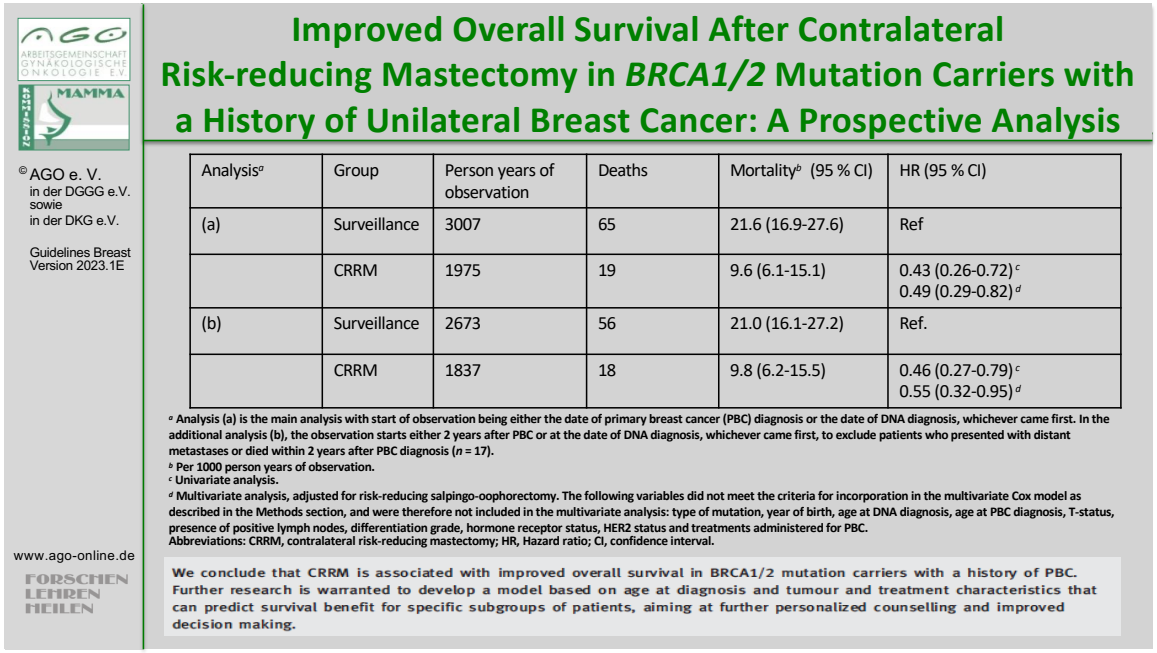

Improved Overall Survival After Contralateral Risk-reducing Mastectomy in *BRCA1/2* Mutation Carriers with a History of Unilateral Breast Cancer: A Prospective Analysis

Guidelines Breast
Version 2023.1E

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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FORSCHEN
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HEILEN

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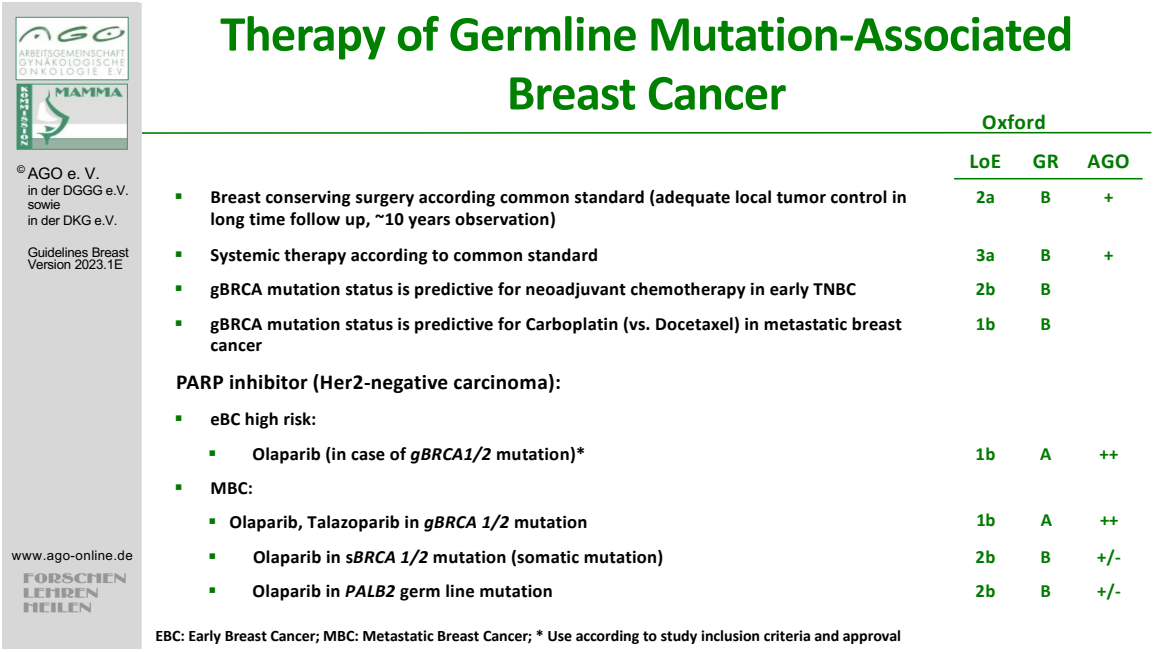

BCS bei BRCA 1/2 Mutationsträgern

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Carboplatin mBC:

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PARP-inhibitors eBC high-risk

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PARP-inhibitors mBC

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PARP-inhibitors mBC gPALB2mut

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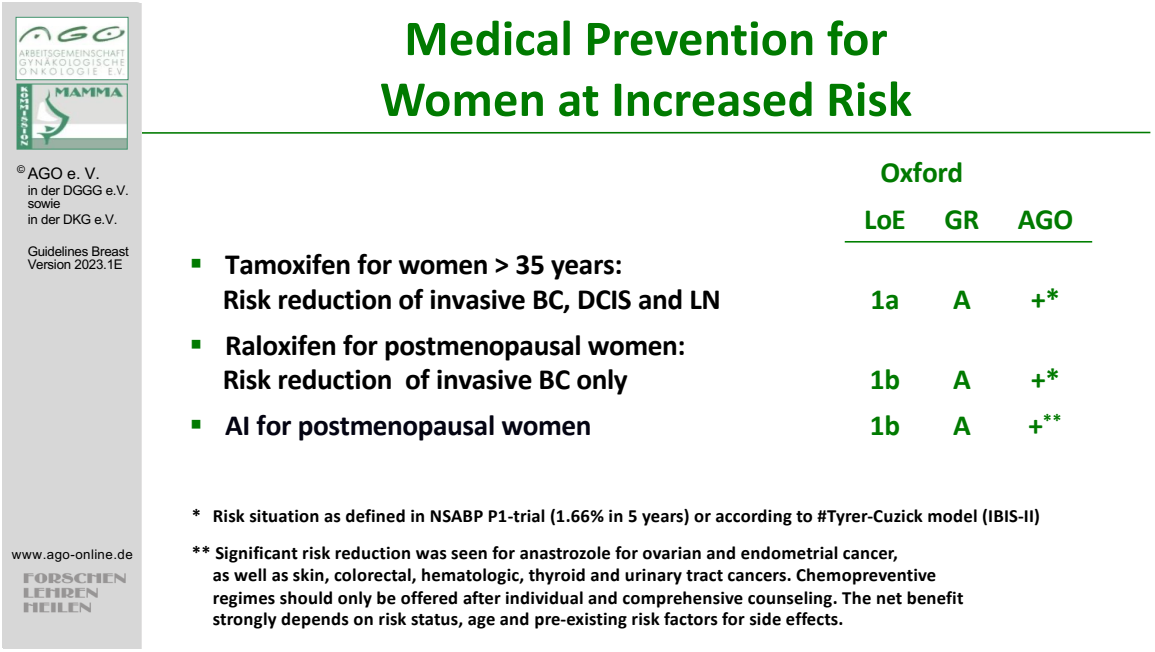

Medical Prevention for Women at Increased Risk

	Oxford		
	LoE	GR	AGO
▪ **Tamoxifen for women > 35 years: Risk reduction of invasive BC, DCIS and LN**	1a	A	+*
▪ **Raloxifen for postmenopausal women: Risk reduction of invasive BC only**	1b	A	+*
▪ **AI for postmenopausal women**	1b	A	+**

* Risk situation as defined in NSABP P1-trial (1.66% in 5 years) or according to #Tyrer-Cuzick model (IBIS-II)

** Significant risk reduction was seen for anastrozole for ovarian and endometrial cancer, as well as skin, colorectal, hematologic, thyroid and urinary tract cancers. Chemopreventive regimes should only be offered after individual and comprehensive counseling. The net benefit strongly depends on risk status, age and pre-existing risk factors for side effects.

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