Guidelines Breast
Version 2022.1D

# Brustkrebsrisiko, Genetik und Prävention

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# Brustkrebsrisiko und Prävention

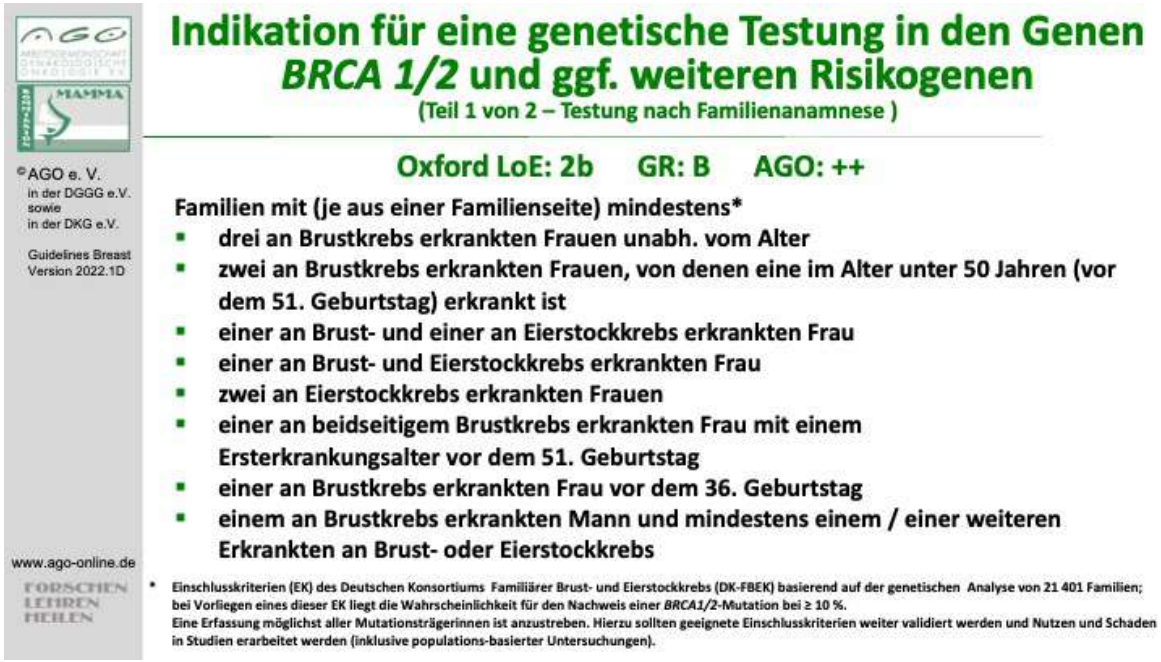
- **Versionen 2003–2021:**
  **Albert / Bischoff / Blohmer / Ditsch / Fasching / Fehm / Kiechle / Maass / Müller-Schimpfle / Mundhenke / Park-Simon / Rhiem / Rody / Schmidt / Schmutzler / Stickeler / Thomssen / Witzel**

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

# Allgemeine Prinzipien in der Prävention

- **Frauen mit einem erhöhten Erkrankungsrisiko für Brustkrebs sind Ratsuchende und nicht Patientinnen.**
- **Dem Angebot präventiver Maßnahmen geht eine umfassende und ausführliche Beratung mit Nutzen / Risikoabwägung voraus.**
- **Das Nichtschadensprinzip steht dabei im Vordergrund.**

***(Primum nil nocere)***





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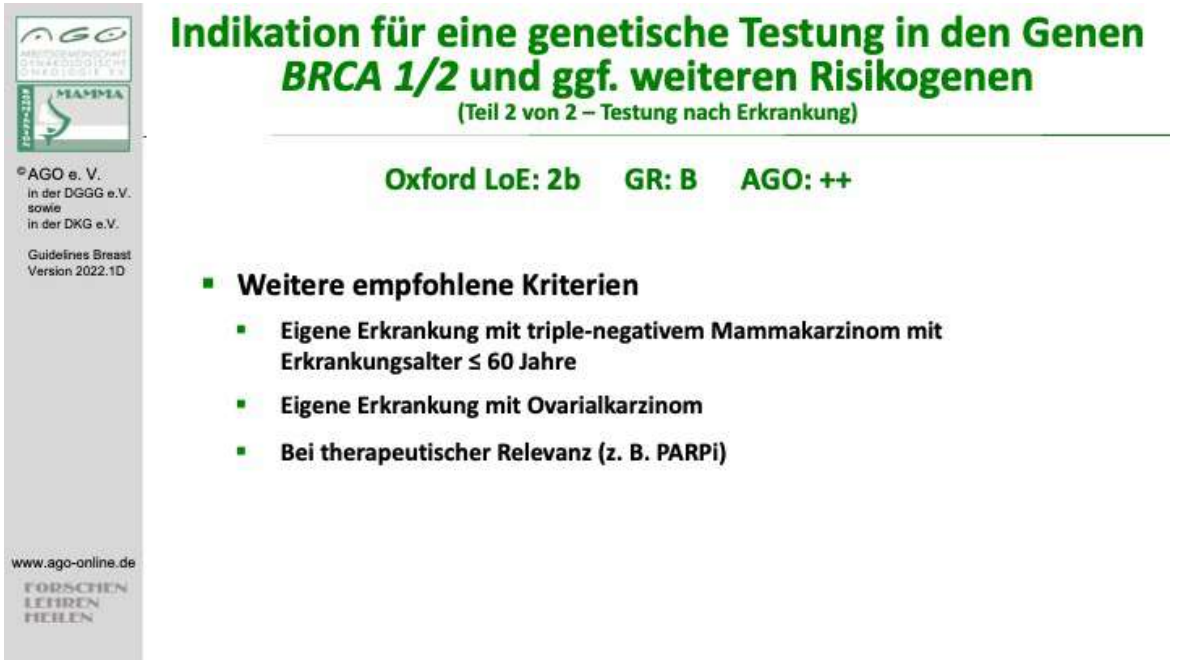



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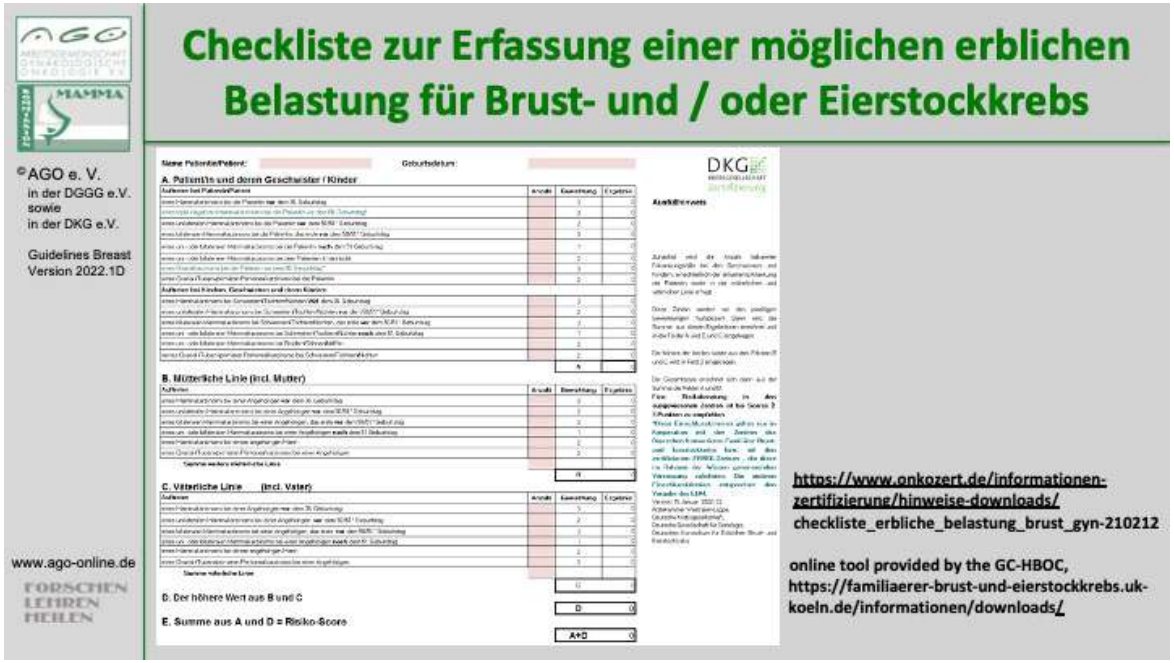


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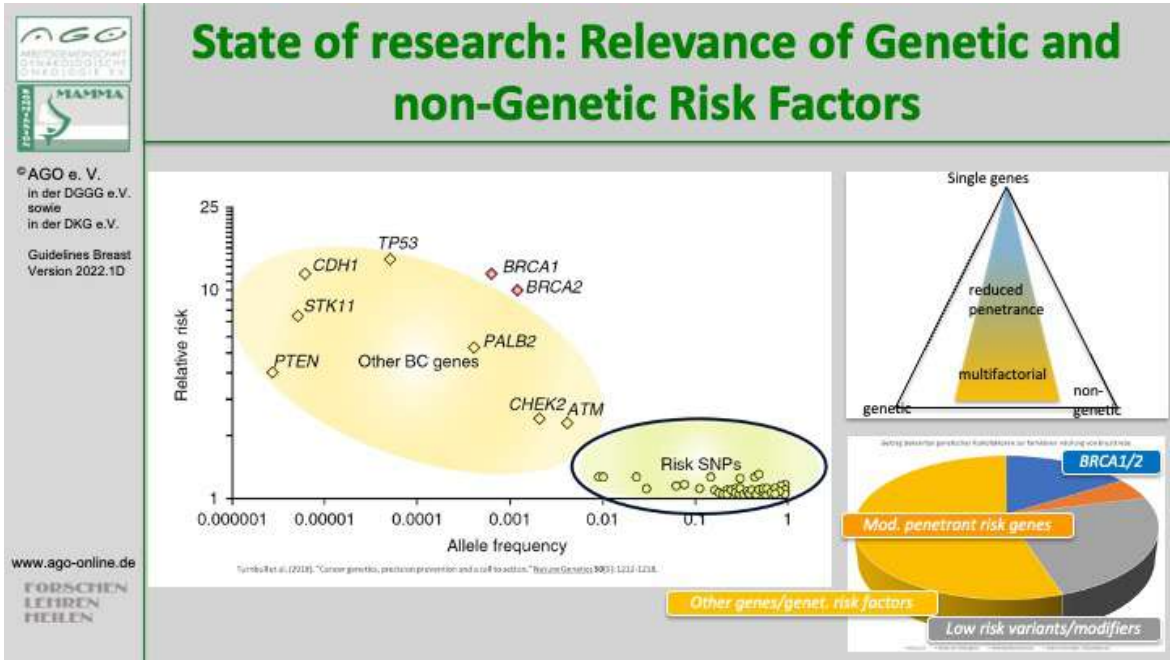



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# Breast Cancer Risk Category



Guidelines Breast
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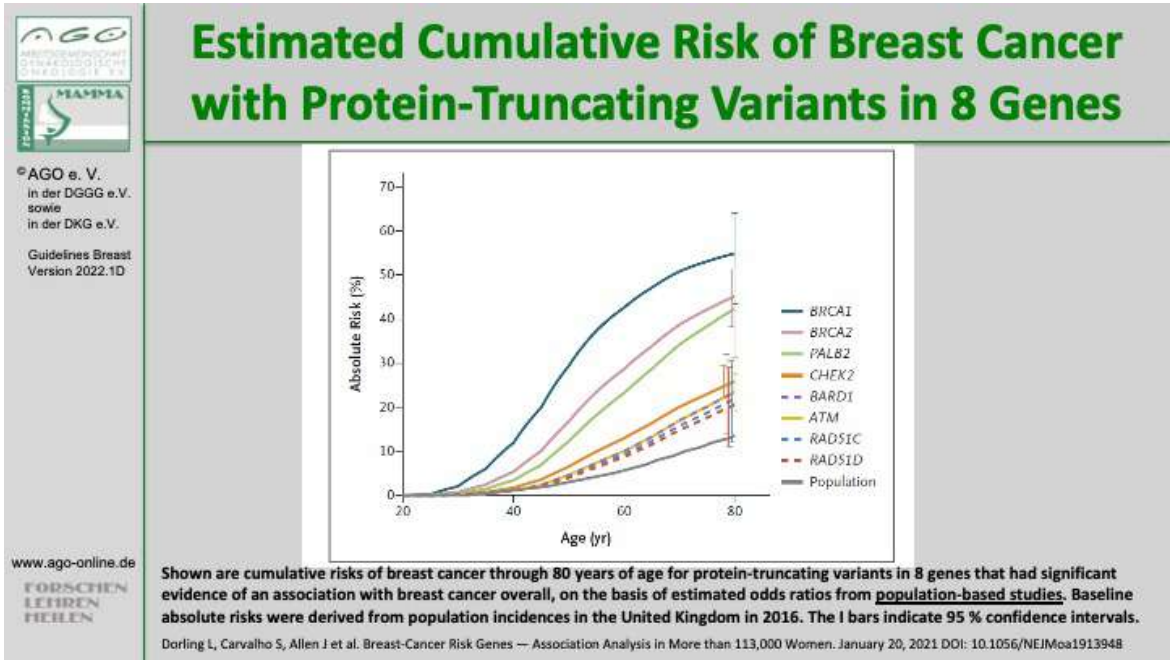
Breast cancer risk category

| | 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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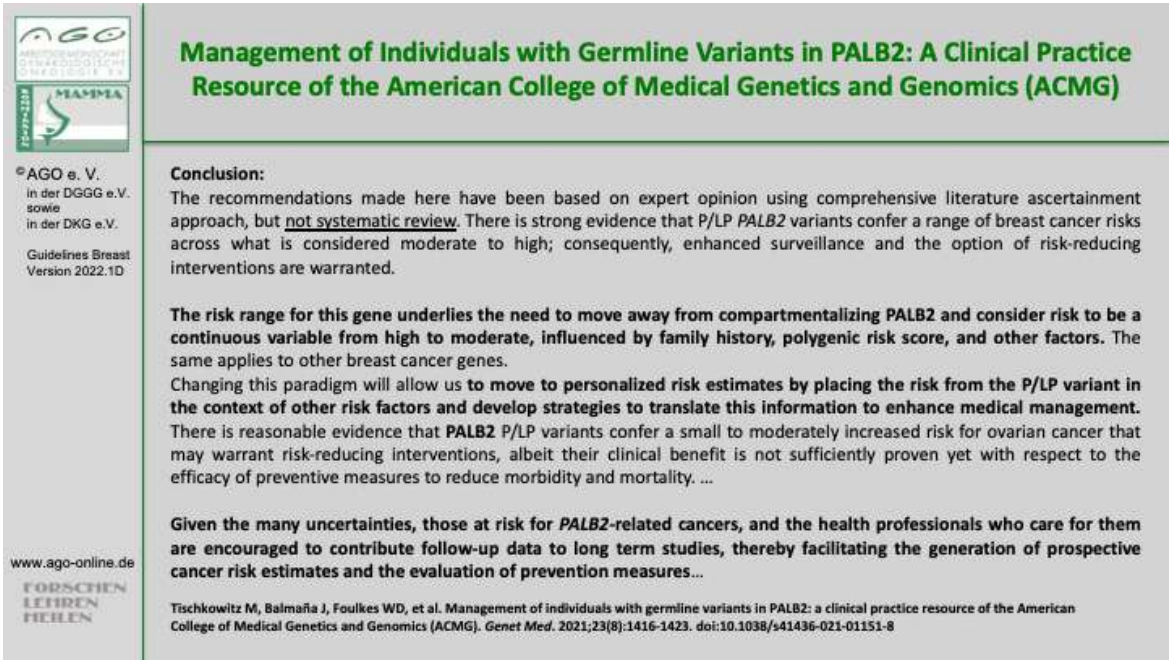


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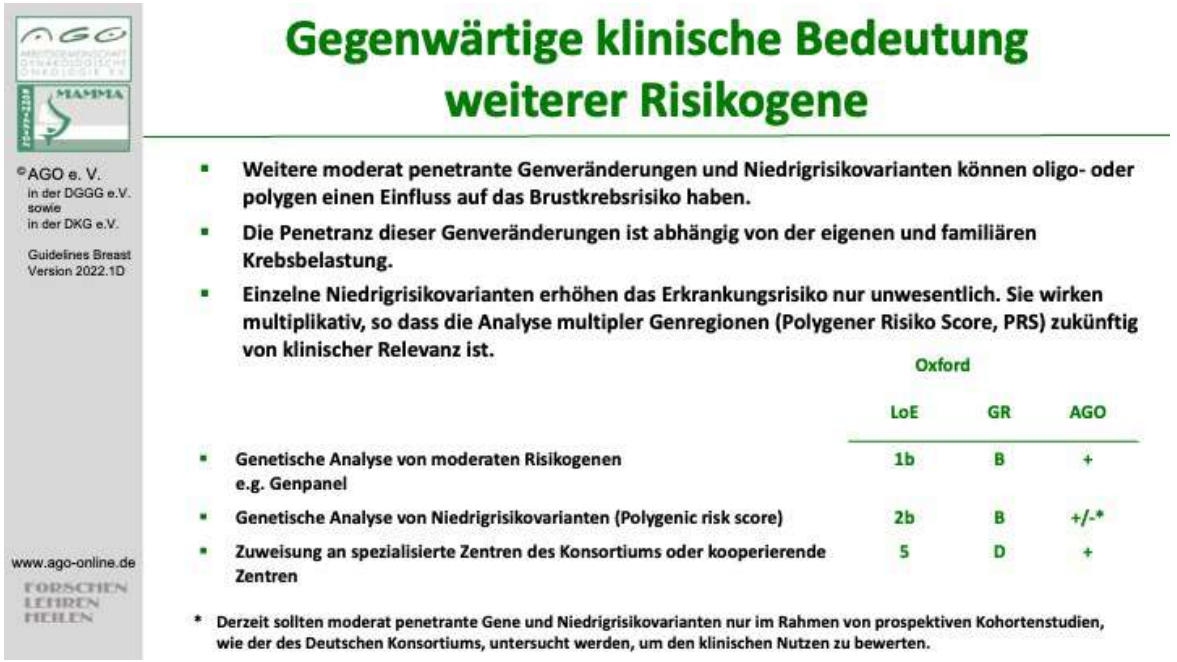



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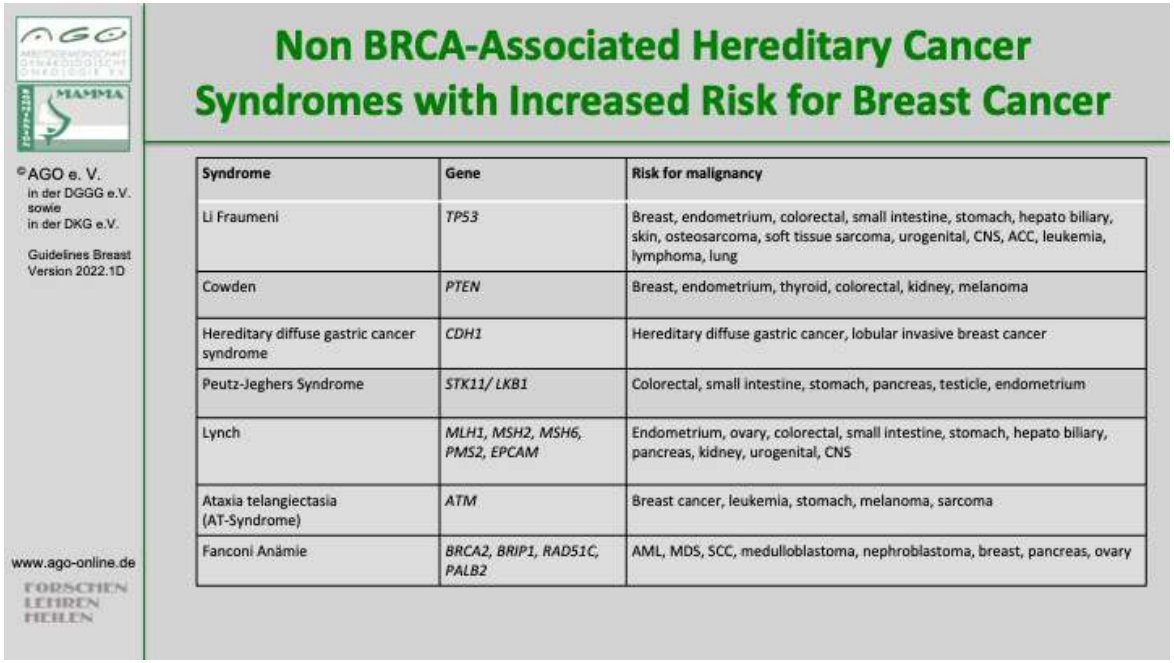


## Non BRCA-Associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer

| 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 |
| Fanconi Anämie | *BRCA2, BRIP1, RAD51C, PALB2* | AML, MDS, SCC, medulloblastoma, nephroblastoma, breast, pancreas, ovary |


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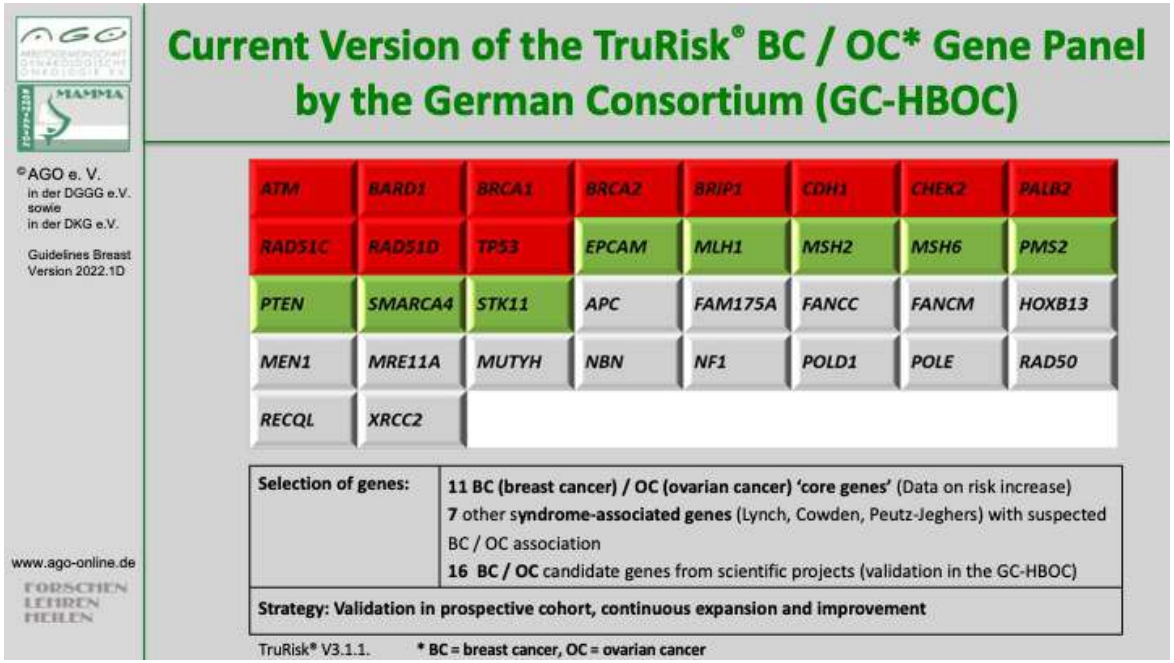
Current Version of the TruRisk® BC / OC* Gene Panel by the German Consortium (GC-HBOC)
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Guidelines Breast
Version 2022.1D
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BARD1
BRCA1
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BRIP1
CDH1
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
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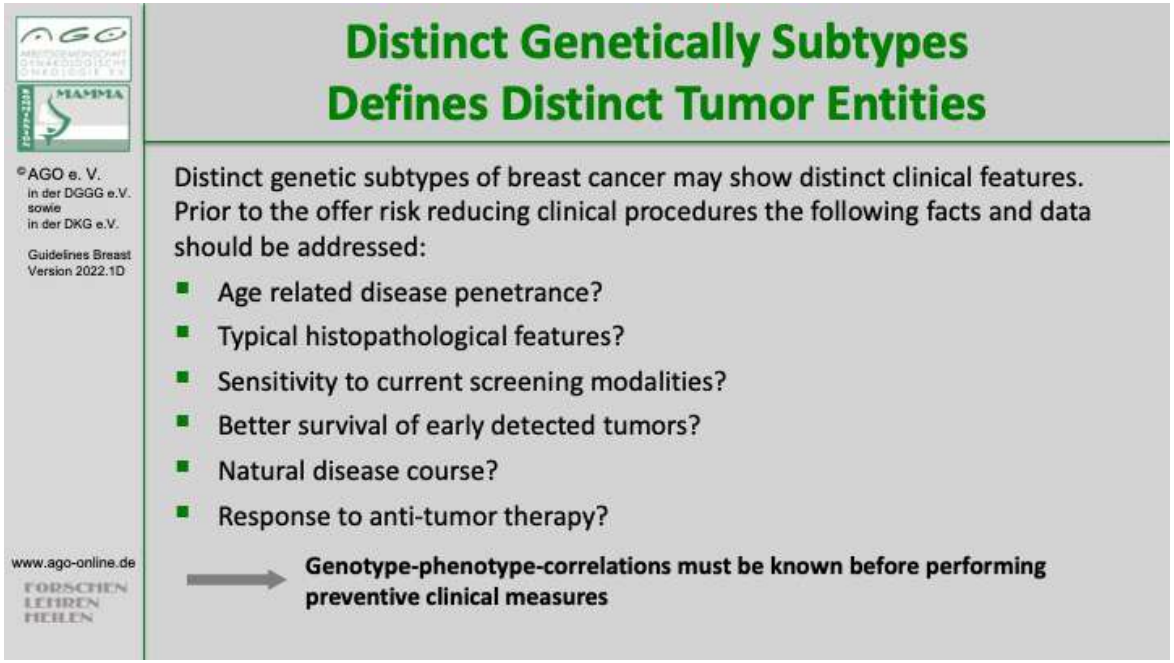
* BC = breast cancer, OC = ovarian cancer





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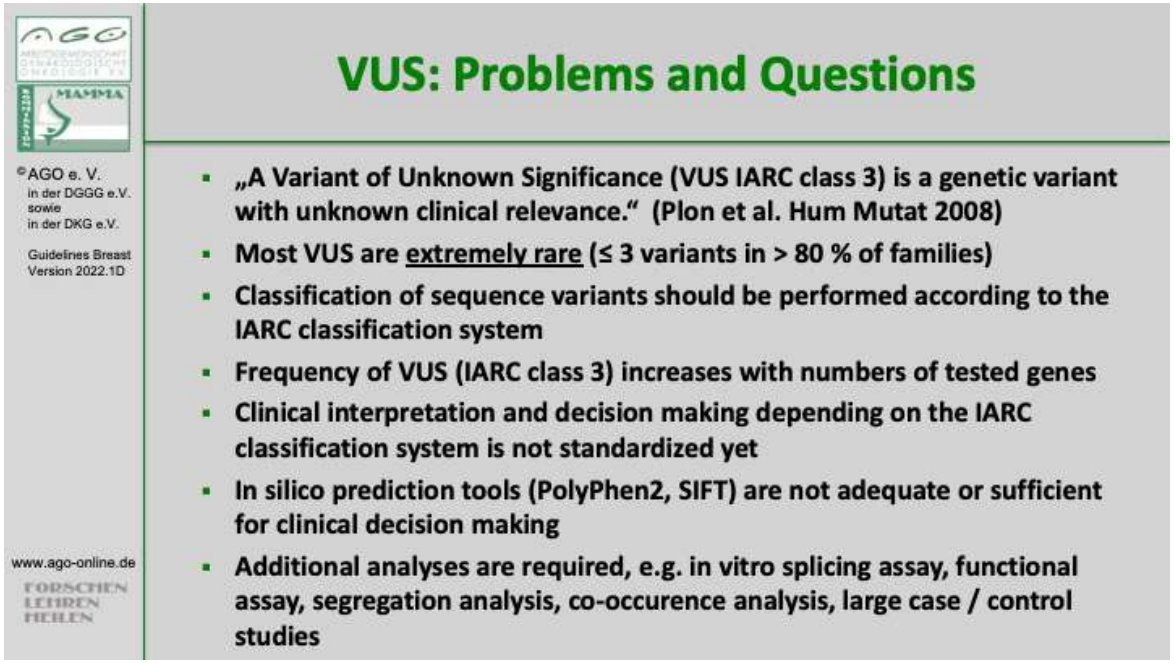



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# Klassifikation der Varianten nach IARC (Plon et al., Human Mutation, 2008)

| Proposed Classification System for Sequence Variants Identified by Genetic Testing | | |
|---|---|---|
| **Class** | **Discription** | **Probability 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 no of clinical significance | < 0,001 |

**Nur Klasse 4 und 5 Varianten gelten als klinisch relevant.**

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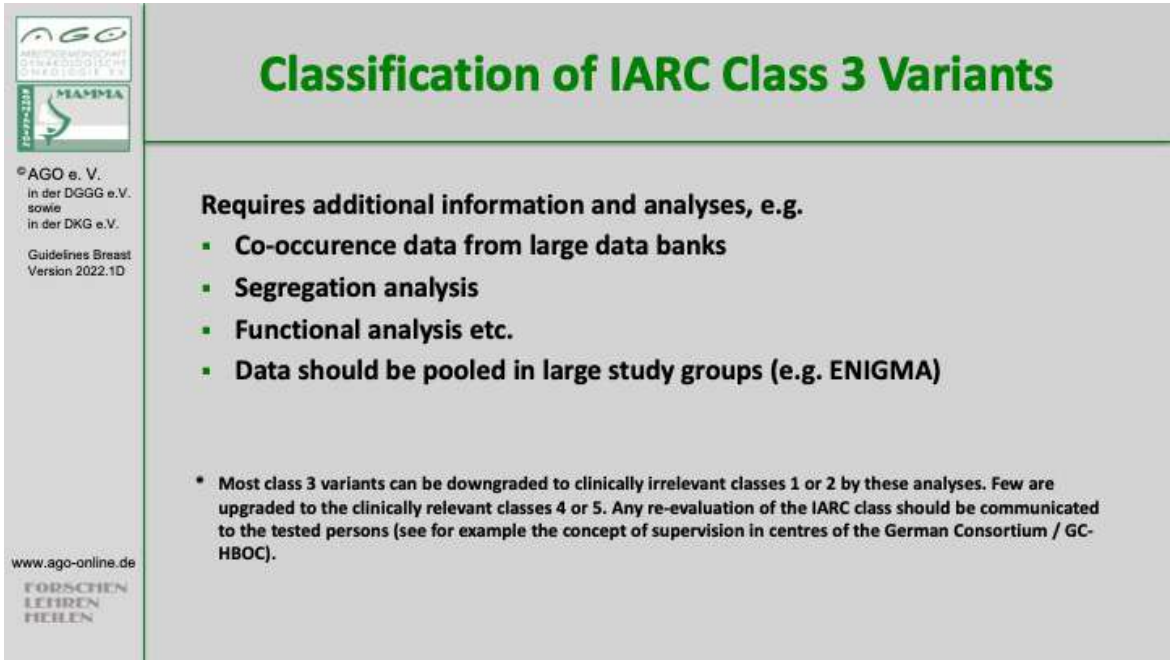


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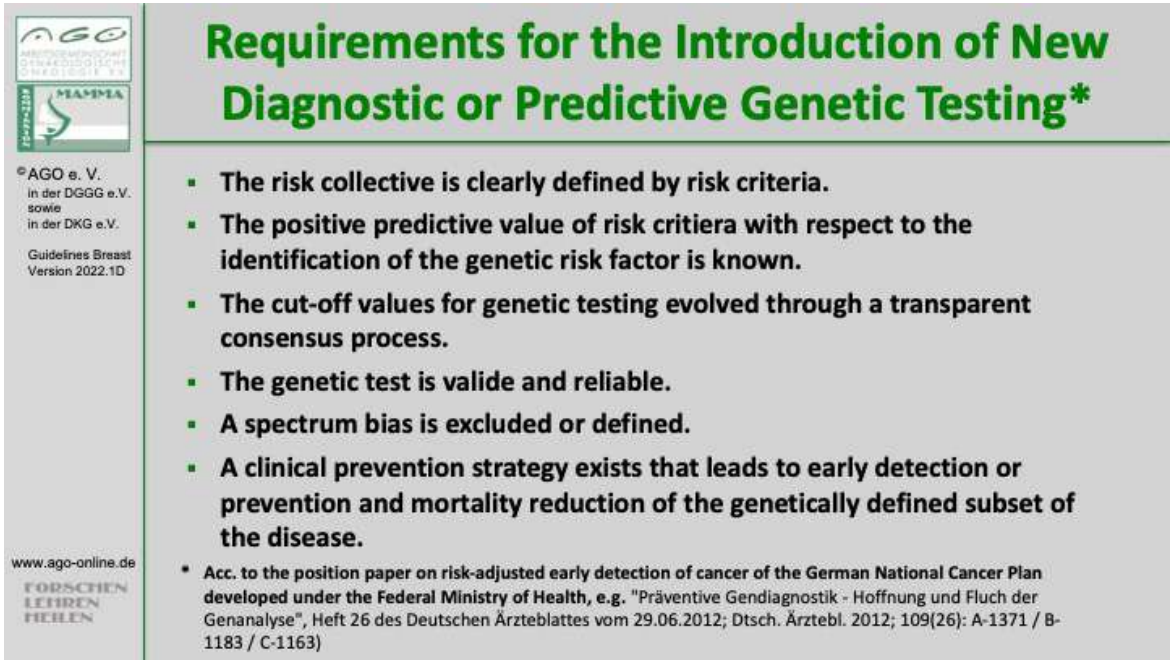



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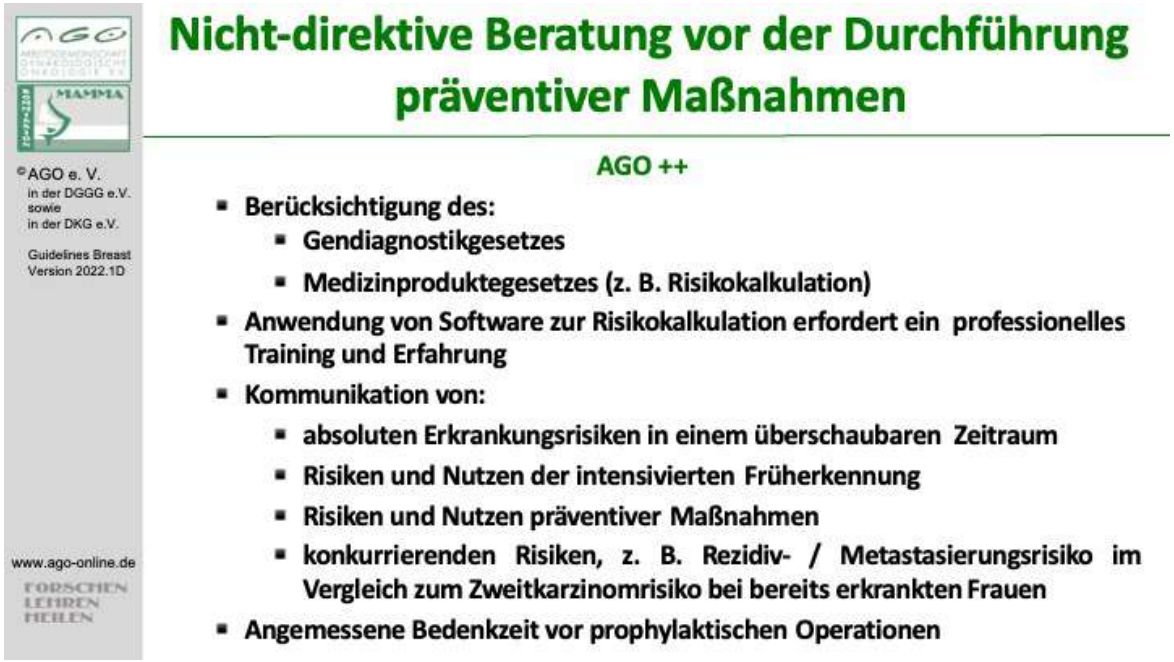


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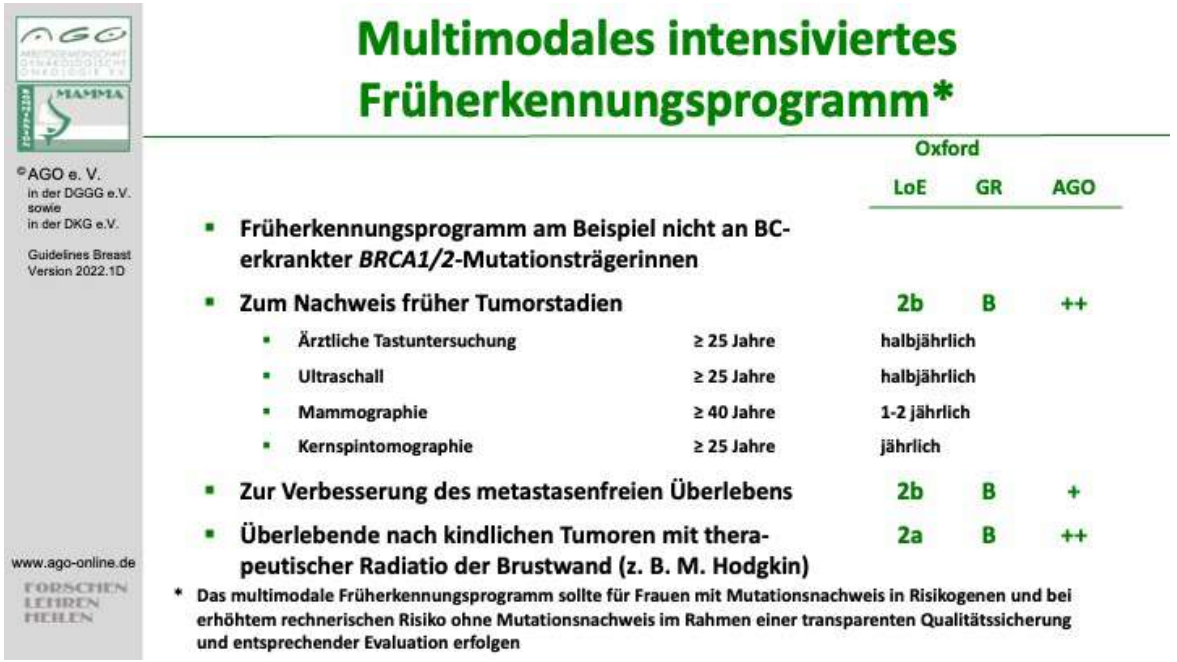



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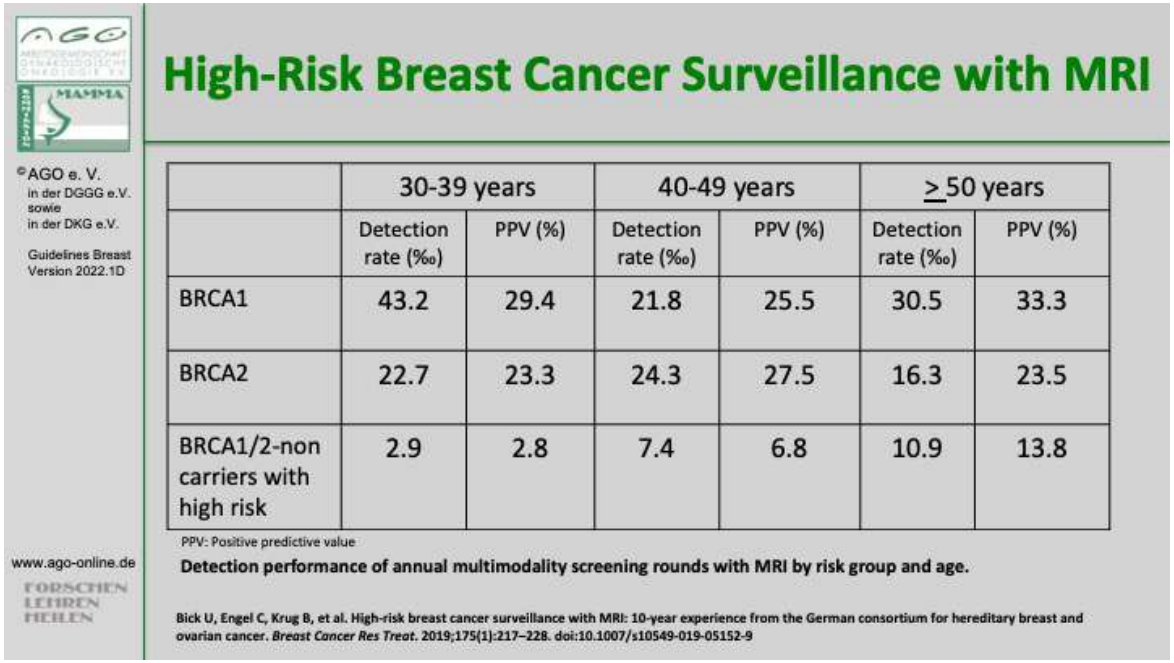


## High-Risk Breast Cancer Surveillance with MRI

| | 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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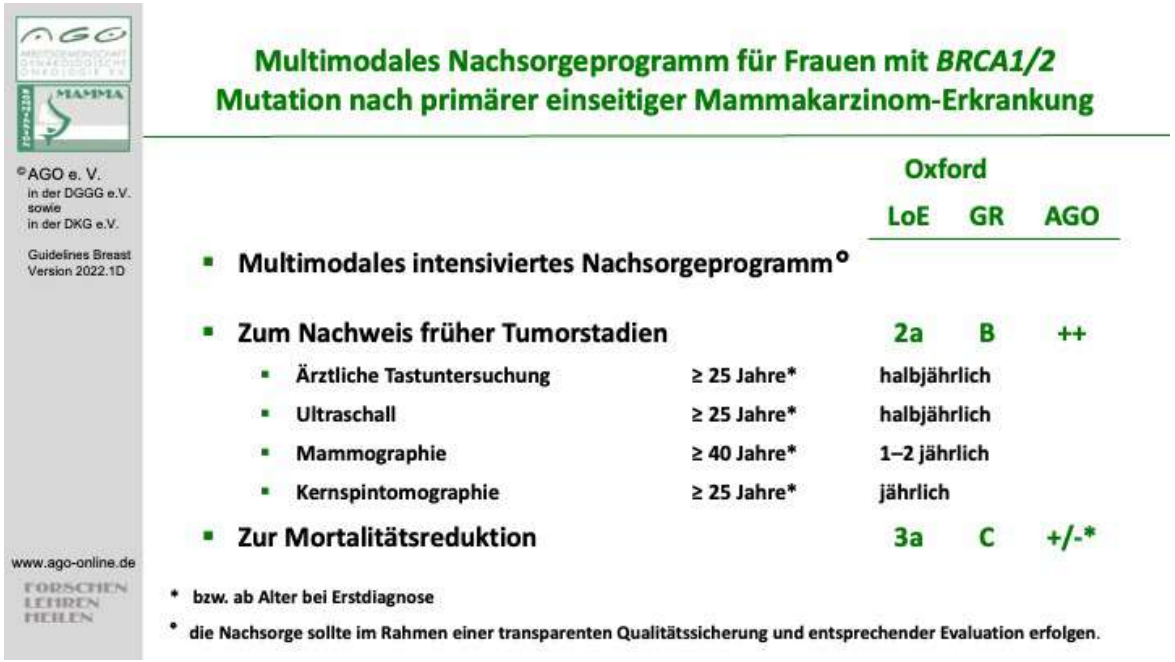



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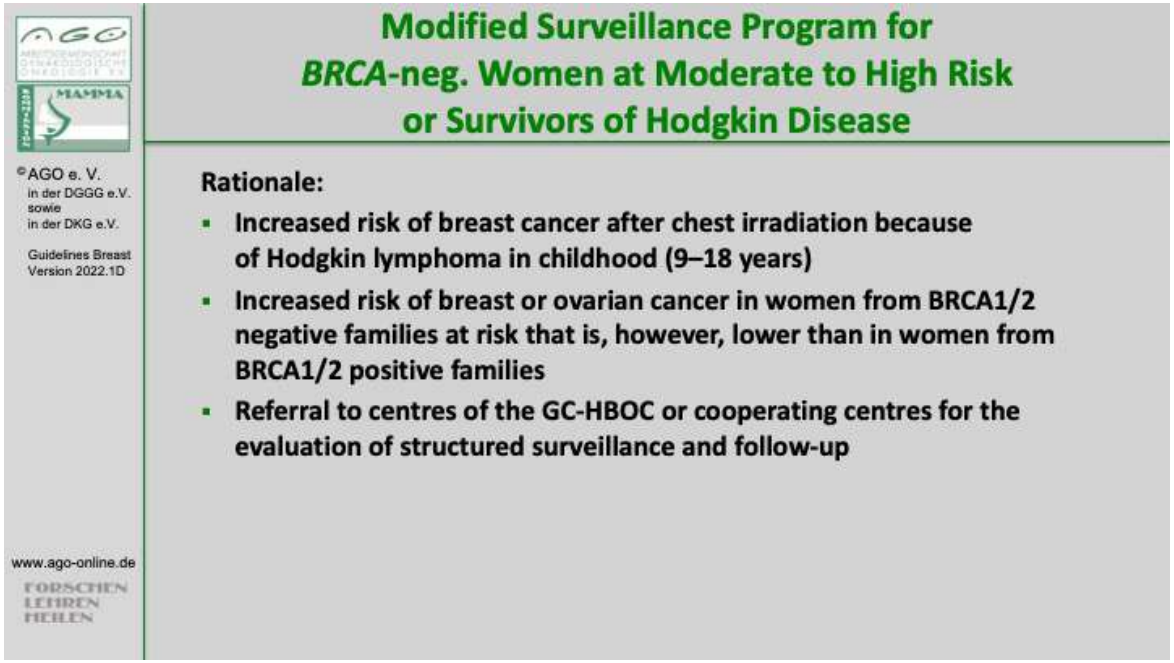



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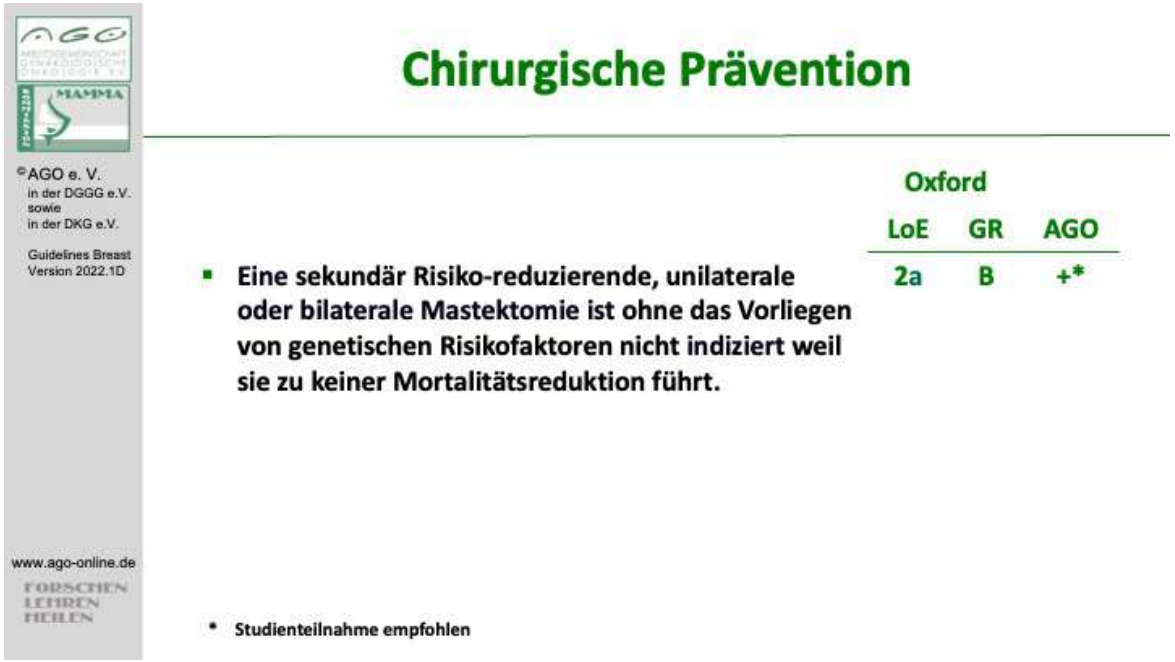



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## Risiko-reduzierende Interventionen bei erkrankten *BRCA1/2* Mutationsträgerinnen

| | Oxford LoE | GR | AGO |
|---|---|---|---|
| ▪ Risikoreduzierende Salpingo-Oophorektomie (RRSO) | 2b | B | +* |
| ▪ reduziert Eierstockkrebsinzidenz und -mortalität | | | |
| ▪ reduziert die Gesamtmortalität (gegensätzliche Ergebnisse bzgl. kontralateraler Brustkrebsinzidenz) | | | |
| ▪ Risikoreduzierende kontralaterale Mastektomie (RRCM)* reduziert kontralaterale Brustkrebsinzidenz und die Mortalität | 2b | B | +* |
| ▪ Tamoxifen (reduziert kontralaterale Brustkrebsinzidenz) | 2b | B | +/-* |
| ▪ Indikationsstellung für RRCM sollte Alter, Ersterkrankungsalter und betroffenes Gen berücksichtigen. | 2a | B | ++* |
| ▪ Risikoreduzierende bilaterale Mastektomie nach Ovarialkarzinom | 4 | C | +/-** |

* Gesamtprognose muss berücksichtigt werden, Studienteilnahme empfohlen
** in Abhängigkeit vom Tumorstadium (FIGO I/II), rezidivfreier Zeit (≥ 5 Jahre), Alter


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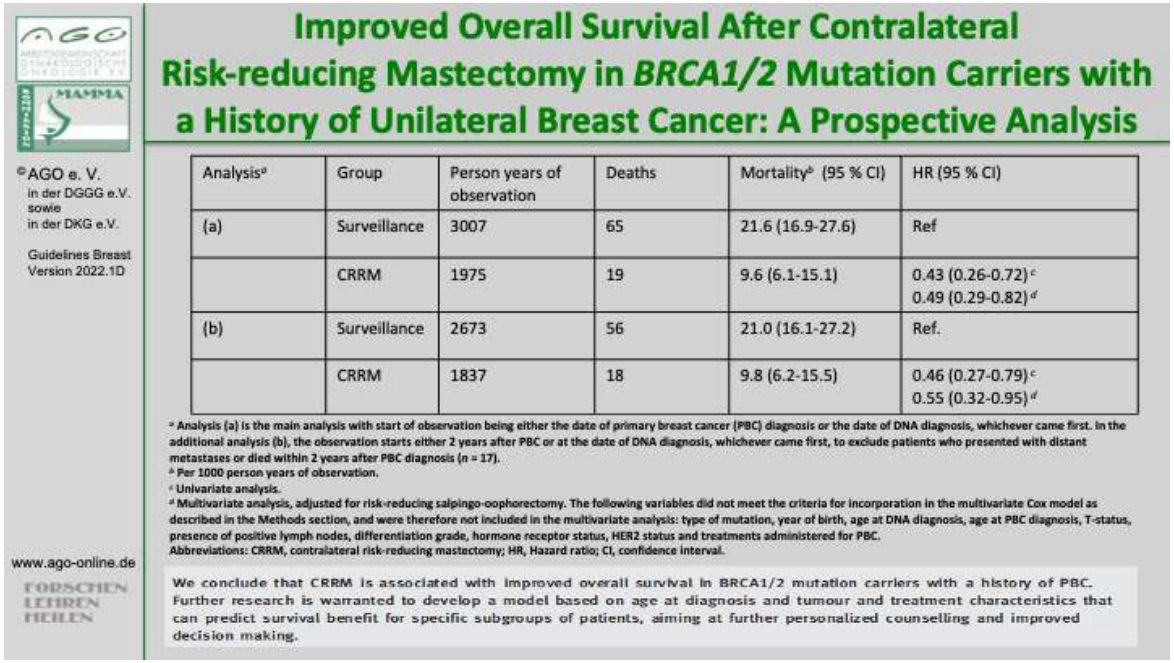


## Improved Overall Survival After Contralateral Risk-reducing Mastectomy in *BRCA1/2* Mutation Carriers with a History of Unilateral Breast Cancer: A Prospective Analysis

| 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]<br>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]<br>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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## Therapie des *Keimbahnmutations*-assoziierten Mammakarzinoms

| Es liegen prospektive Kohortenstudien mit begrenzter Nachbeobachtungszeit vor | Oxford LoE | GR | AGO |
|---|---|---|---|
| ▪ Brusterhaltende Operation: Adäquate lokale Tumorkontrolle (~ 10 Jahre Follow-up) | 2a | B | + |
| ▪ Systemische Therapie nach den allgemeinen Standards | 3a | B | + |
| ▪ gBRCA Mutationsstatus ist ein prädiktiver Faktor für das Ansprechen auf Chemotherapie bei TNBC | 2b | B | + |
| ▪ Carboplatin (vs. Docetaxel) beim metast. MaCa | 2b | B | + |
| PARP-Inhibitor (Her2-negative Karzinome): | | | |
| ▪ EBC : Olaparib (bei *gBRCA1/2*-Mutation)* | 1b | B | + |
| ▪ MBC: | | | |
| ▪ *gBRCA1/2*-Mutation | | | |
| ▪ Olaparib | 1b | A | ++ |
| ▪ Talazoparib | 1b | A | ++ |
| ▪ Somatische *BRCA1/2*-Mutation (Keimbahntestung *gBRCA* ist Standard) | | | |
| ▪ Olaparib | 2b | B | +/- |
| ▪ *PALB2*-Keimbahnmutation | | | |
| ▪ Olaparib | 2b | B | +/- |

EBC: Early Breast Cancer; MBC: Metastatic Breast Cancer; * Einsatz gemäß Studieneinschlusskriterien und Zulassung

**BCS bei BRCA 1/2 Mutationsträgern**


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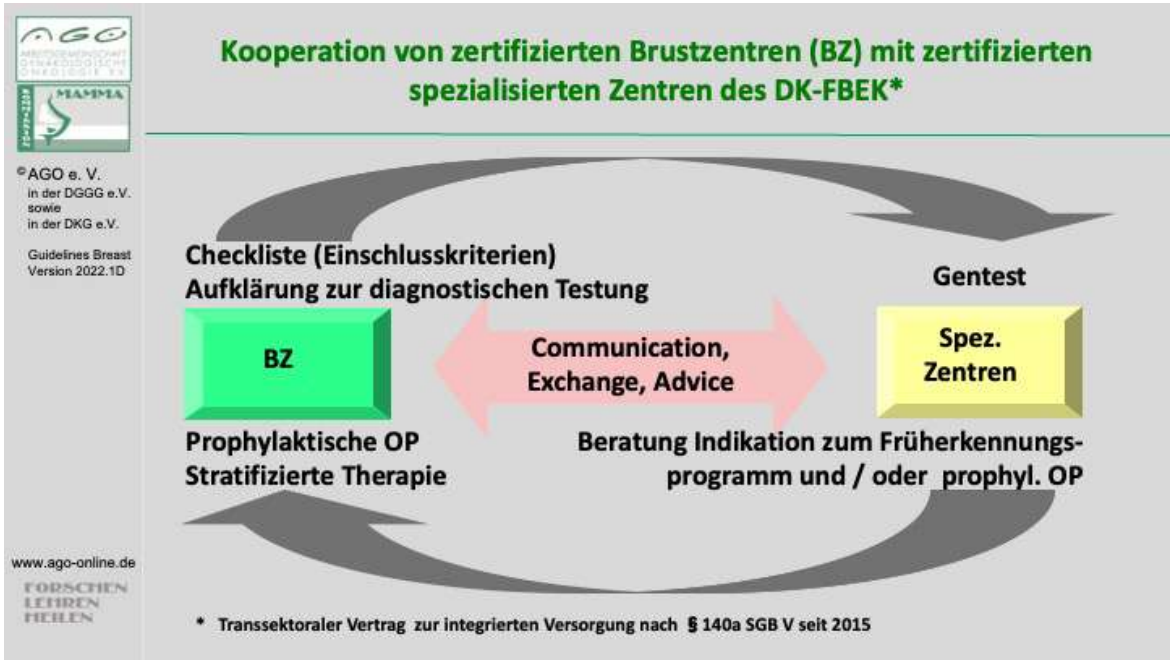
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