© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2021.1E

FORSCHEN
LEHREN
HEILEN

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Breast Cancer Risk and Prevention

Breast Cancer Risk and Prevention

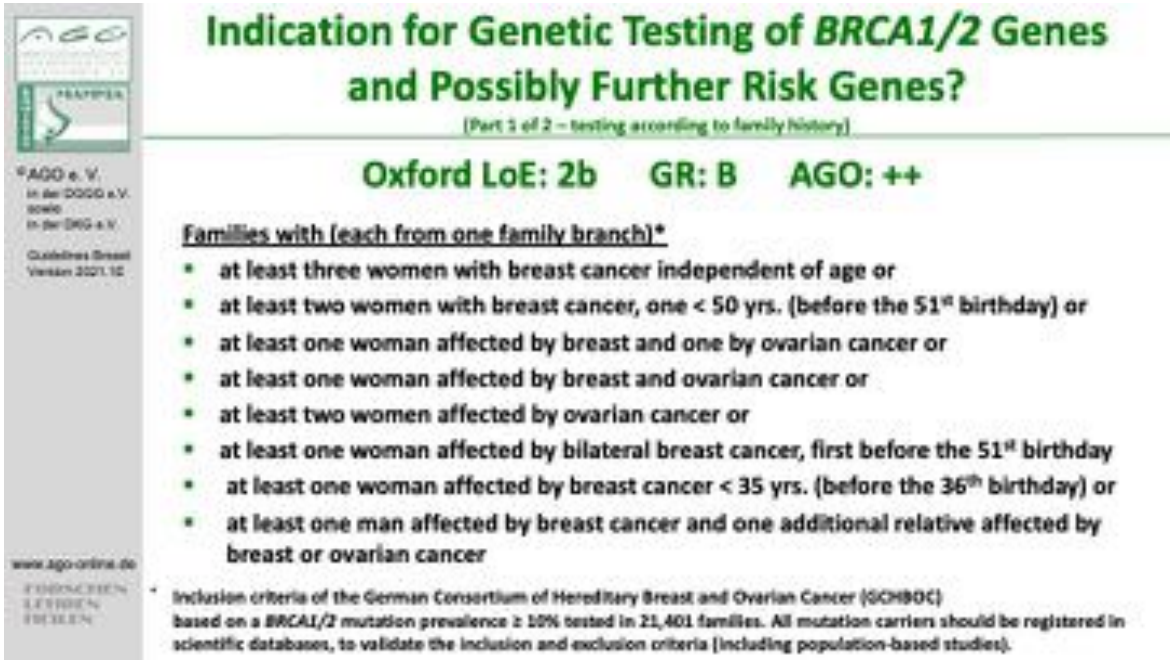
- **Versions 2003–2020:**
  Schmutzler mit Albert / Bischoff / Blohmer / Ditsch / Fasching / Fehm / Kiechle / Maass / Müller-Schimpfle / Mundhenke / Rhiem / Rody / Schmidt / Schmutzler / Stickeler / Thomssen

- **Version 2021:**
  Park-Simon / Witzel

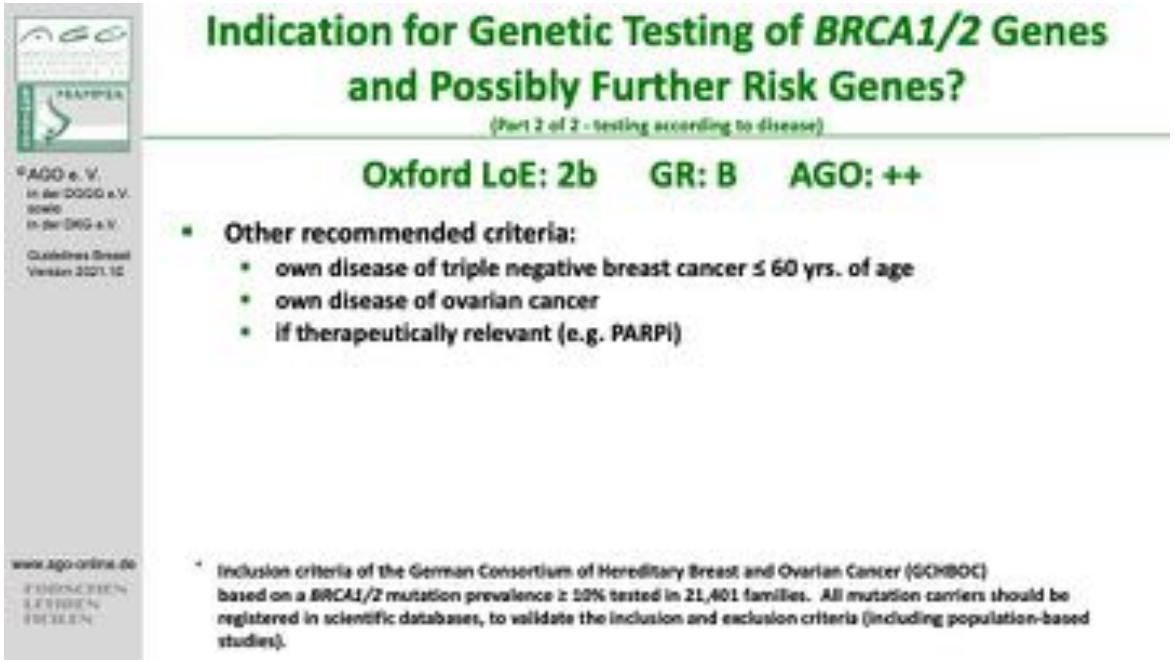
Principles of Prevention

- **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)



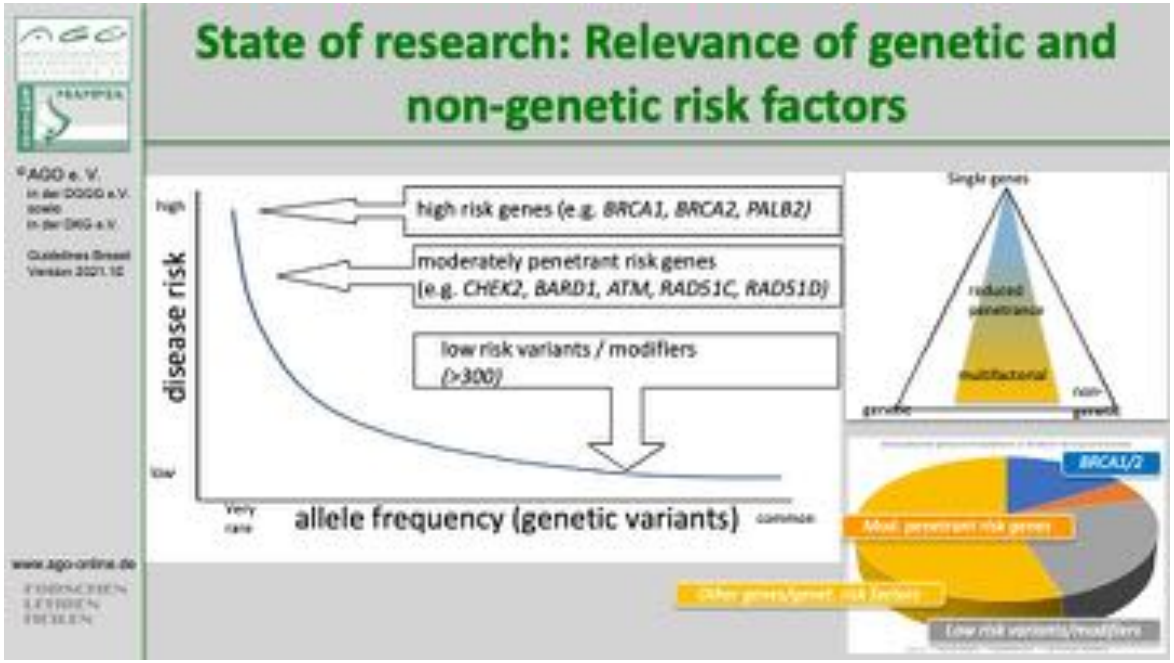
1. Couch FJ, Hart SN, Sharma P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. J Clin Oncol. 2015;33(4):304-11.
2. Meindl A, German Consortium for Hereditary B, Ovarian C. Comprehensive 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.
3. 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.
4. Manchanda R, Gaba F. Population Based Testing for Primary Prevention: A Systematic Review.Cancers (Basel). 2018 Nov 5;10(11).
5. Beitsch PD, Whitworth PW, Hughes K. Underdiagnosis of Hereditary Breast Cancer: Are Genetic Testing Guidelines a Tool or an Obstacle? Journal of Clinical Oncology 2019 37:6, 453-460



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. 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.
3. Hahnen E, Lederer B, Hauke J et al. Germline Mutation Status, Pathological Complete Response, and Disease-Free Survival in Triple-Negative Breast Cancer: Secondary Analysis of the GeparSixto Randomized Clinical Trial. JAMA Oncol. 2017 Oct 1;3(10):1378-1385. doi: 10.1001/jamaoncol.2017.1007. PMID: 28715532; PMCID: PMC5710508.
4. Harter P, Hauke J, Heitz F, et al. Prevalence of deleterious germline variants in risk genes including BRCA1/2 in consecutive ovarian cancer patients (AGO-TR1). PLoS One 2017;12:e0186043.
5. 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
6. Litton JK, Hurvitz SA, Mina LA, et al. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. Ann Oncol. 2020 Nov;31(11):1526-1535. doi: 10.1016/j.annonc.2020.08.2098. Epub 2020 Aug 20. PMID: 32828825.
7. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation N Engl J Med

2017;377:523-533
8. Manchanda R, Gaba F. Population Based Testing for Primary Prevention: A Systematic Review. Cancers (Basel). 2018 Nov 5;10(11).

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



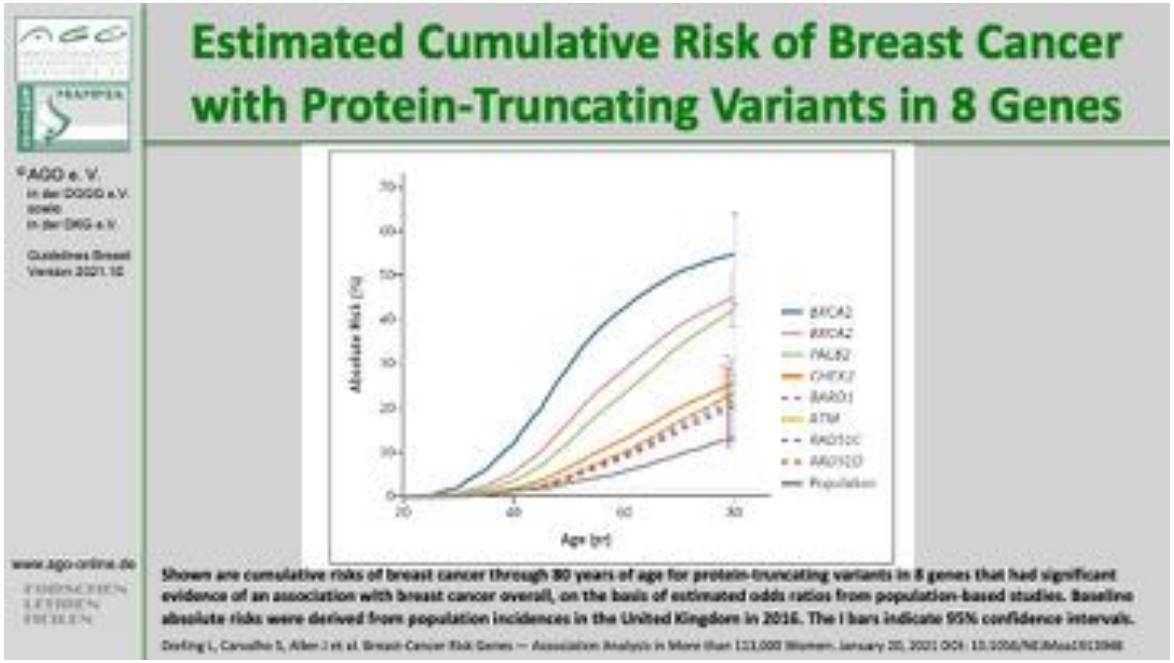
1. Couch FJ, Shimelis H, Hu C, et al. Associations between cancer predisposition testing panel genes and breast cancer JAMA Oncol 2017;3:1190-1196.
2. Couch FJ, Nathanson KL, Offit K. Two decades after BRCA: setting paradigms in personalized cancer care and prevention. Science. 2014;343(6178):1466-70.
3. Hauke J, Horvath J, Groß E, et al. Gene panel testing of 5589 BRCA1/2-negative index patients with breast cancer in a routine diagnostic setting: results of the German Consortium for Hereditary Breast and Ovarian Cancer. Cancer Med. 2018 Mar 9. doi: 10.1002/cam4.1376.
4. Castera L, Harter V, Muller E. et al.: Landscape of pathogenic variations in a panel of 34 genes and cancer risk estimation from 5131 HBOC families. Genetics in Medicine. Genet Med. 2018 Jul 10. doi: 10.1038/s41436-018-0005-9.
5. Ghoussaini M, Fletcher O, Michailidou K et al. Genome-wide association analysis identifies three new breast cancer susceptibility loci. Nat Genet 2012; 44: 312–318
6. Michailidou K, Hall P, Gonzalez-Neira A et al. Large-scale genotyping identifies 41 new loci associated with breast cancer risk. Nat Genet 2013; 45: 353–361, 361e1–361e2
7. 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: 373–380

8. Milne RL, Kuchenbaecker KB, Michailidou K et al. Identification of ten variants associated with risk of estrogen-receptor-negative breast cancer. Nat Genet 2017; 49: 1767–1778
9. Michailidou K, Lindstrom S, Dennis J et al. Association analysis identifies 65 new breast cancer risk loci. Nature 2017; 551: 92–94
10. Fachal L, Aschard H, Beesley J, Barnes DR, Allen J, Kar S, Pooley KA, Dennis J, Michailidou K, Turman C et al: Fine-mapping of 150 breast cancer risk regions identifies 191 likely target genes. Nat Genet 2020.
11. Dorling L, Carvalho S, Allen J et al. Breast-Cancer Risk Genes — Association Analysis in More than 113,000 Women. NEJM 2021 DOI: 10.1056/NEJMoa1913948

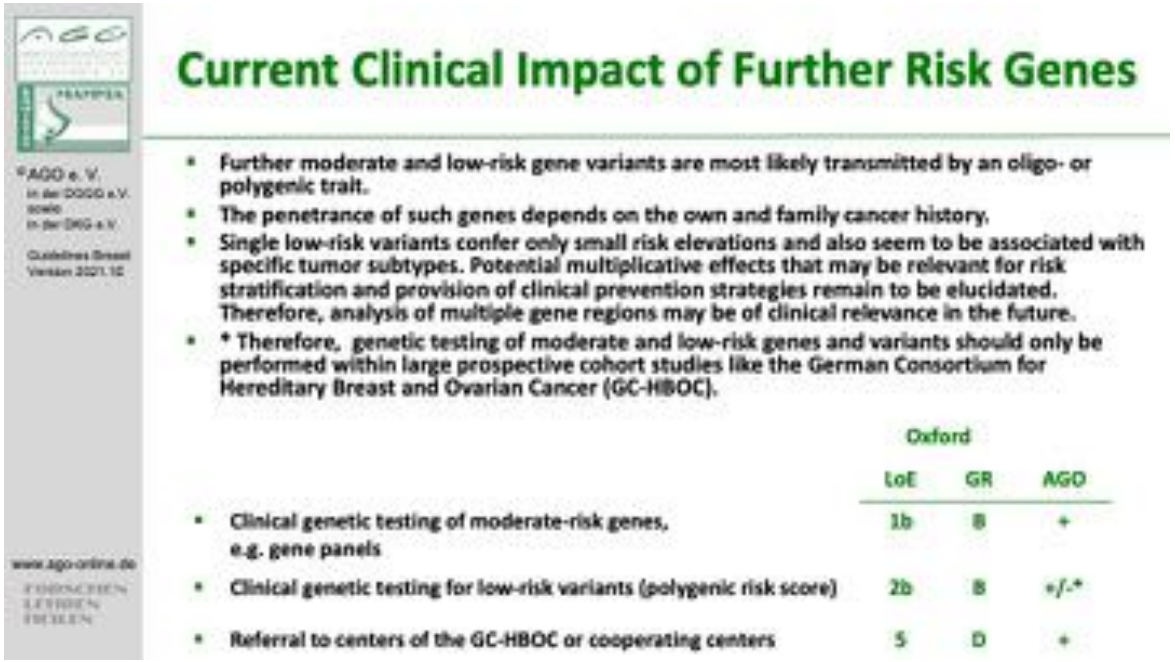
1. Antoniou AC, Casadei S, Heikkinen T, et al. Breast-cancer risk in families with mutations in PALB2. N Engl J Med. 2014;371(6):497-506.
2. Buys SS, Sandbach JF, Gammon A, et al. A study of over 35,000 women with breast cancer tested with a 25-gene panel of hereditary cancer genes. Cancer 2017 May 15;123(10):1721-1730. doi: 10.1002/cncr.30498. Epub 2017 Jan 13
3. 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
4. Couch FJ, Shimelis H, Hu C, et al. Associations between cancer predisposition testing panel genes and breast cancer JAMA Oncol 2017;3:1190-1196.
5. Couch FJ, Nathanson KL, Offit K. Two decades after BRCA: setting paradigms in personalized cancer care and prevention. Science. 2014;343(6178):1466-70.
6. Hauke J, Horvath J, Groß E, et al. Gene panel testing of 5589 BRCA1/2-negative index patients with breast cancer in a routine diagnostic setting: results of the German Consortium for Hereditary Breast and Ovarian Cancer. Cancer Med. 2018 Apr;7(4):1349-1358. doi: 10.1002/cam4.1376. Epub 2018 Mar 9.
7. Shimelis H, LaDuca, Hu C et al.: Triple-negative breast cancer risk genes identified by multigene hereditary cancer panel testing. J Natl Cancer Inst 2018 Aug 7.doi:10.1093/jnci/djy106.
8. Southey MC, Goldgar DE, Winqvist R et al. PALB2, CHEK2 and ATM rare variants and cancer risk: data from COGS. J Med Genet. 2016

Dec;53(12):800-811. doi: 10.1136/jmedgenet-2016-103839. Epub 2016 Sep 5. PMID: 27595995; PMCID: PMC5200636.

9. Yang X, Song H, Leslie G et al. Ovarian and Breast Cancer Risks Associated With Pathogenic Variants in RAD51C and RAD51D. J Natl Cancer Inst. 2020 Dec 14;112(12):1242-1250. doi: 10.1093/jnci/djaa030. PMID: 32107557; PMCID: PMC7735771.
10. Yang X, Leslie G, Doroszuk A et al. Cancer Risks Associated With Germline PALB2 Pathogenic Variants: An International Study of 524 Families. J Clin Oncol. 2020 Mar 1;38(7):674-685. doi: 10.1200/JCO.19.01907. Epub 2019 Dec 16. PMID: 31841383; PMCID: PMC7049229.
11. 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
12. https://www.konsortium-familiaerer-brustkrebs.de/konsensusempfehlung/, last accessed 21th January 2021



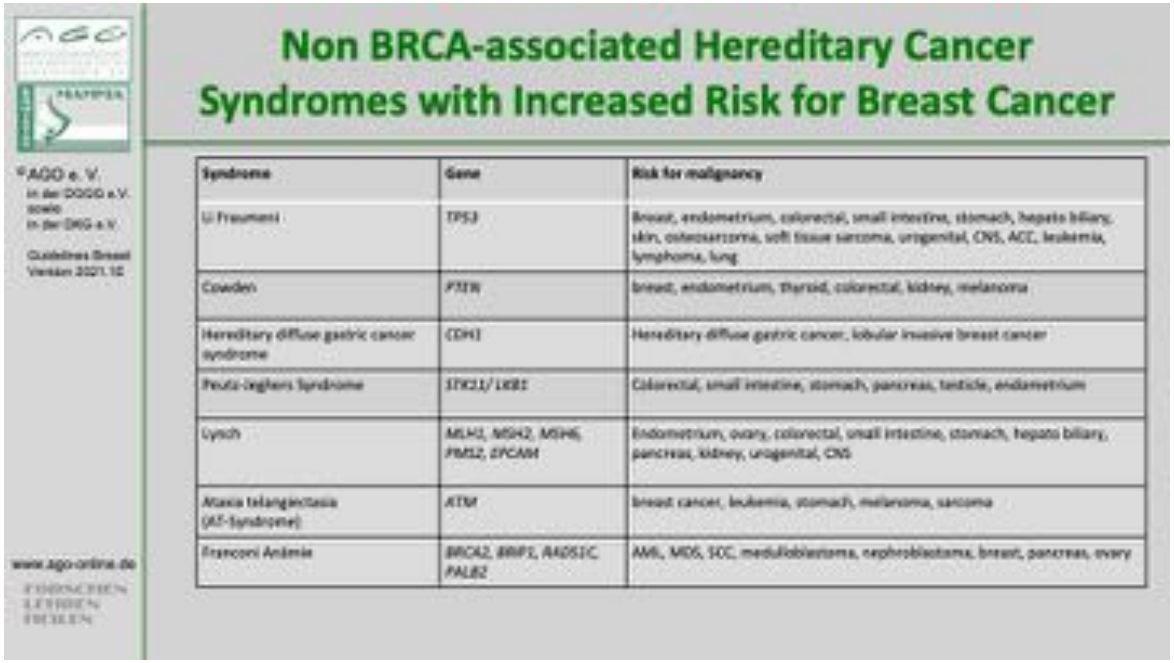
1. Dorling L, Carvalho S, Allen J et al. Breast-Cancer Risk Genes — Association Analysis in More than 113,000 Women. January 20, 2021 DOI: 10.1056/NEJMoa1913948



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.
2. Couch FJ, Shimelis H, Hu C, et al. Associations between cancer predisposition testing panel genes and breast cancer JAMA Oncol 2017;3:1190-1196.
3. Cuzick J, Brentnall AR, Segal C, et al. Impact of a Panel of 88 Single Nucleotide Polymorphisms on the Risk of Breast Cancer in High-Risk Women: Results From Two Randomized Tamoxifen Prevention Trials. J Clin Oncol. 2016:JCO2016698944.
4. Dunning AM, Michailidou K, Kuchenbaecker KB, et al. Breast cancer risk variants at 6q25 display different phenotype associations and regulate ESR1, RMND1 and CCDC170. Nat Genet. 2016;48(4):374-86.
5. 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
6. Hauke J, Horvath J, Groß E, et al. Gene panel testing of 5589 BRCA1/2-negative index patients with breast cancer in a routine diagnostic setting: results of the German Consortium for Hereditary Breast and Ovarian Cancer. Cancer Med 2018 Apr;7(4):1349-1358. doi: 10.1002/cam4.1376. Epub 2018 Mar 10.
7. Mavaddat N, Pharoah PD, Michailidou K, et al. Prediction of breast cancer risk based on profiling with common genetic variants. J Natl Cancer Inst. 2015;107(5).
8. Mavaddat N, Michailidou K, Dennis J et al. Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. Am J

Hum Genet. 2019 Jan 3;104(1):21-34. doi: 10.1016/j.ajhg.2018.11.002. Epub 2018 Dec 13. PMID: 30554720; PMCID: PMC6323553.

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.



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

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

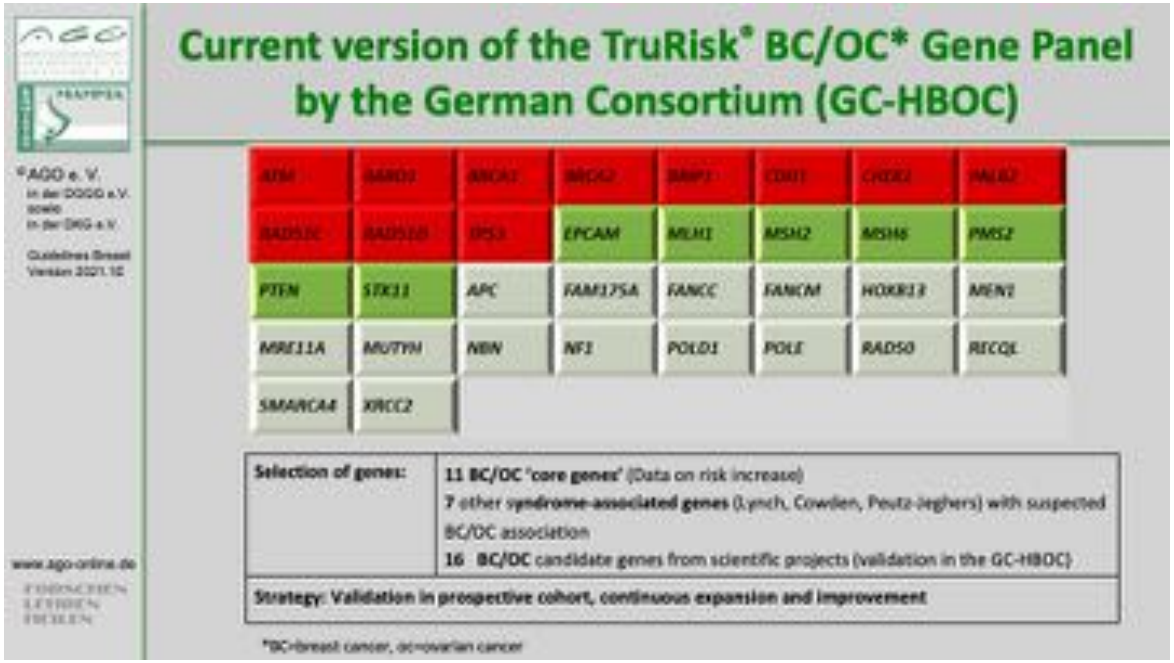
Guidelines Breast
Version 2021.1E

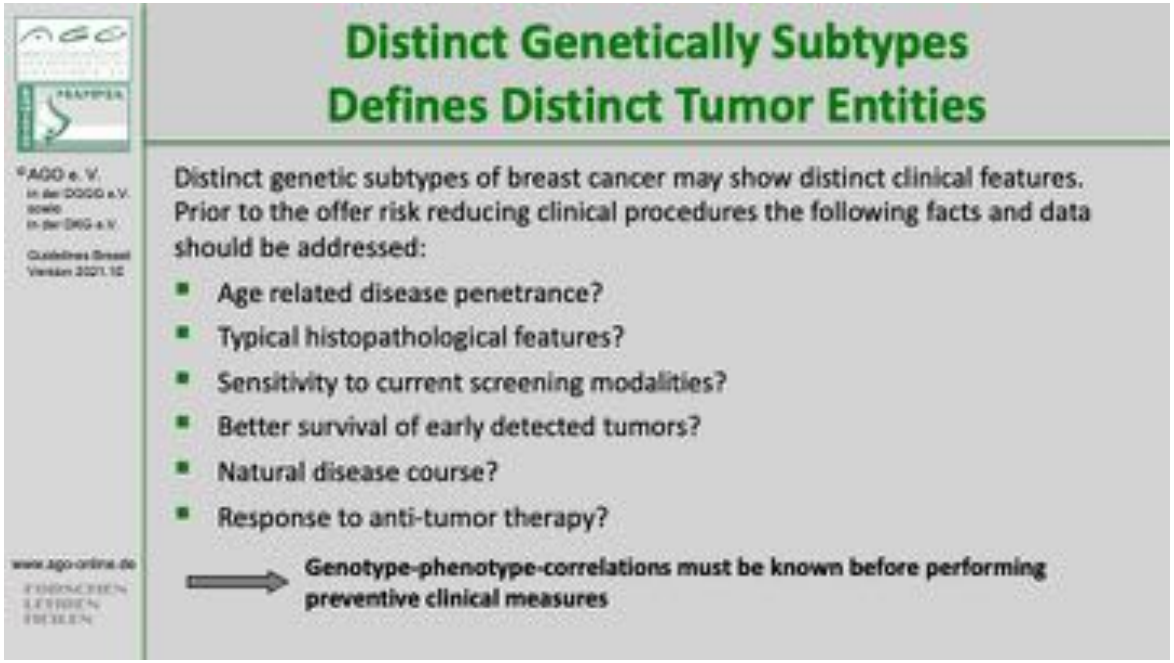
www.ago-online.de

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

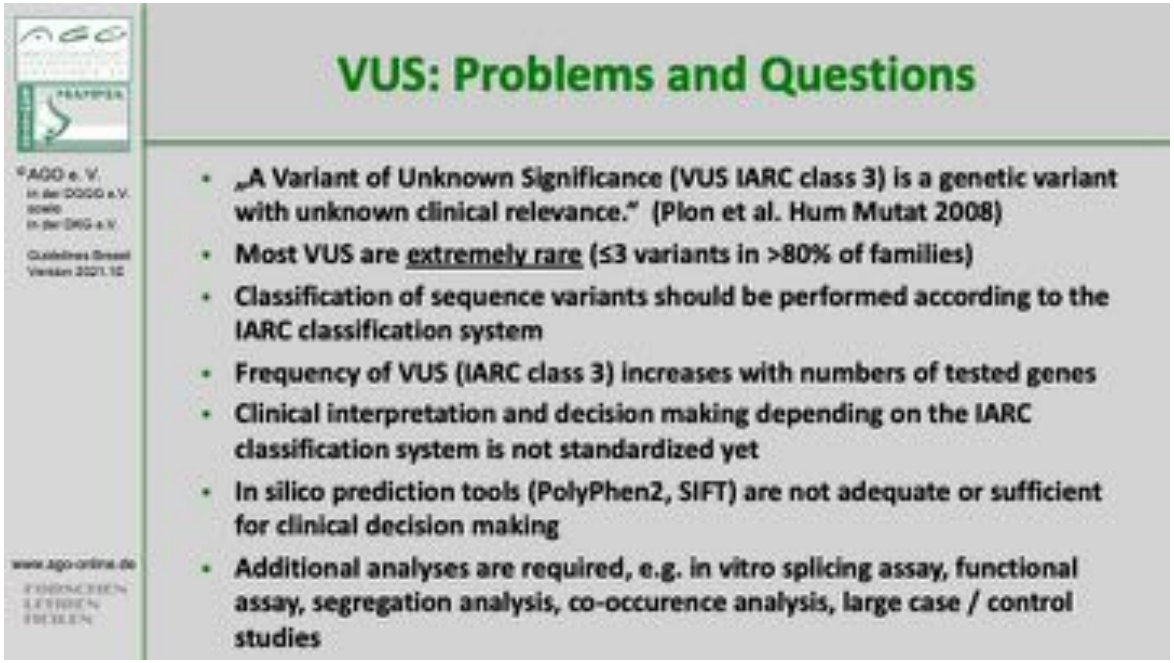
1. di Masi A, Antoccia A. NBS1 Heterozygosity and Cancer Risk. Curr Genomics. 2008;9(4):275-81.
2. Gao P, Ma N, Li M, et al. Functional variants in NBS1 and cancer risk: evidence from a meta-analysis of 60 publications with 111 individual studies. Mutagenesis. 2013;28(6):683-97.
3. Meindl A, Hellebrand 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.
4. Song H, Dicks E, Ramus SJ, et al. Contribution of Germline Mutations in the RAD51B, RAD51C, and RAD51D Genes to Ovarian Cancer in the Population. J Clin Oncol. 2015;33(26):2901-7.
5. Goldgar DE, Healey S, Dowty JG, et al. Rare variants in the ATM gene and risk of breast cancer. Breast Cancer Res. 2011;13(4):R73.
6. Engel C, Loeffler M, Steinke V, et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. J Clin Oncol. 2012;30(35):4409-15.
7. Hearle N, Schumacher V, Menko FH, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. Clin Cancer Res. 2006;12(10):3209-15.
8. 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.
9. Tan MH, Mester JL, Ngeow J, et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res. 2012;18(2):400-7.

10. Masciari S, Dillon DA, Rath M, et al. Breast cancer phenotype in women with TP53 germline mutations: a Li-Fraumeni syndrome consortium effort. Breast Cancer Res Treat. 2012;133(3):1125-30.
11. 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.
12. 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.
13. Couch FJ et al.: Associations between cancer predisposition testing panel genes and breast cancer. JAMA Oncology 2017, DOI: 10.1001/jamaoncol.2017.042
14. Hauke J, Horvath J, Groß E, et al. Gene panel testing of 5589 BRCA1/2-negative index patients with breast cancer in a routine diagnostic setting: results of the German Consortium for Hereditary Breast and Ovarian Cancer. Cancer Med. 2018 Mar 9. doi: 10.1002/cam4.1376.


Current version of the TruRisk® BC/OC* Gene Panel by the German Consortium (GC-HBOC)
© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.
Guidelines Breast
Version 2021.1E
www.ago-online.de
ATM
BARD1
BRCA1
BRCA2
BRIP1
CDH1
CHEK2
PALB2
RAD51C
RAD51D
TP53
EPCAM
MLH1
MSH2
MSH6
PMS2
PTEN
STK11
APC
FAM175A
FANCC
FANCM
HOXB13
MEN1
MRE11A
MUTYH
NBN
NF1
POLD1
POLE
RAD50
RECQL
SMARCA4
XRCC2
Selection of genes:
11 BC/OC '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
*BC=breast cancer, oc=ovarian cancer



1. Pirie A, Guo Q, Kraft P, et al. Common germline polymorphisms associated with breast cancer specific survival. Breast Cancer Res. 2015;17(1):58.
2. Mulligan AM, Couch FJ, Barrowdale D, et al. Common breast cancer susceptibility alleles are associated with tumour subtypes in BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2. Breast Cancer Res. 2011;13(6):R110.
3. Fasching PA, Pharoah PD, Cox A, et al. The role of genetic breast cancer susceptibility variants as prognostic factors. Hum Mol Genet. 2012;21(17):3926-39.
4. Broeks A, Schmidt MK, Sherman ME, et al. Low penetrance breast cancer susceptibility loci are associated with specific breast tumor subtypes: findings from the Breast Cancer Association Consortium. Hum Mol Genet. 2011;20(16):3289-303.
5. Weischer M, Nordestgaard BG, Pharoah P, et al. CHEK2*1100delC heterozygosity in women with breast cancer associated with early death, breast cancer-specific death, and increased risk of a second breast cancer. J Clin Oncol. 2012;30(35):4308-16.



1. Plon SE, Eccles DM, Easton D, et al. Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. Human mutation. 2008;29(11):1282-91.
2. Ernst C, Hahnen E, Engel C, et al. Performance of in silico prediction tools for the classification of rare BRCA1/2 missense variants in clinical diagnostics. *BMC Med Genomics*. 2018;11(1):35. Published 2018 Mar 27. doi:10.1186/s12920-018-0353-y

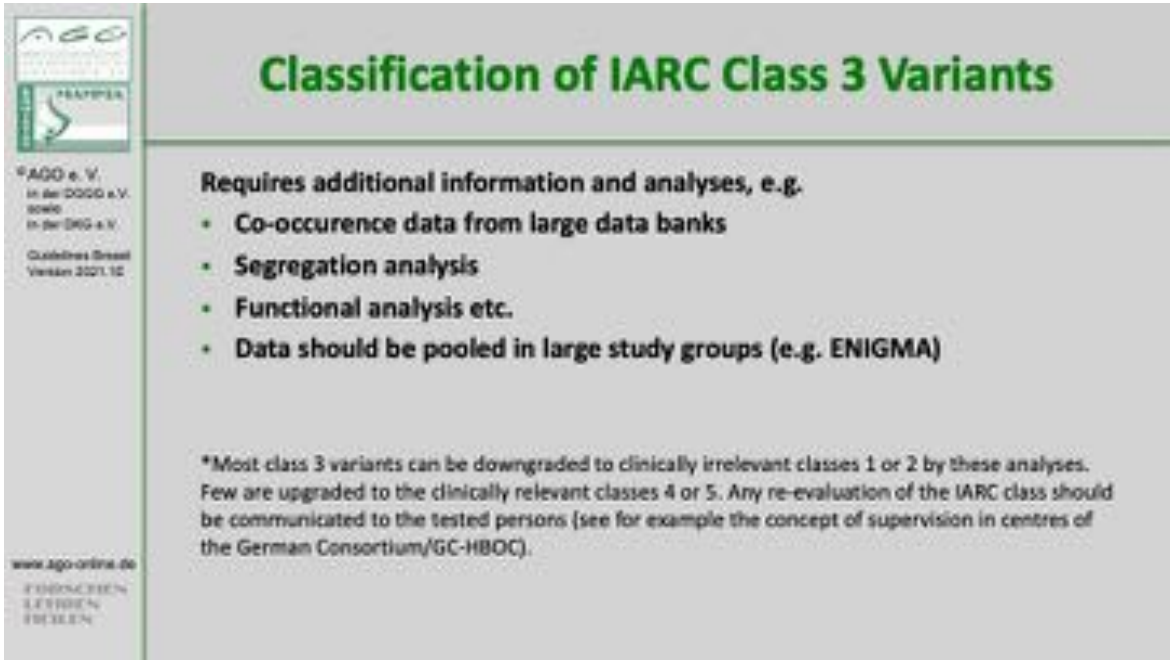
Variant classification proposed by IARC

(Plon et al., Human Mutation, 2008)

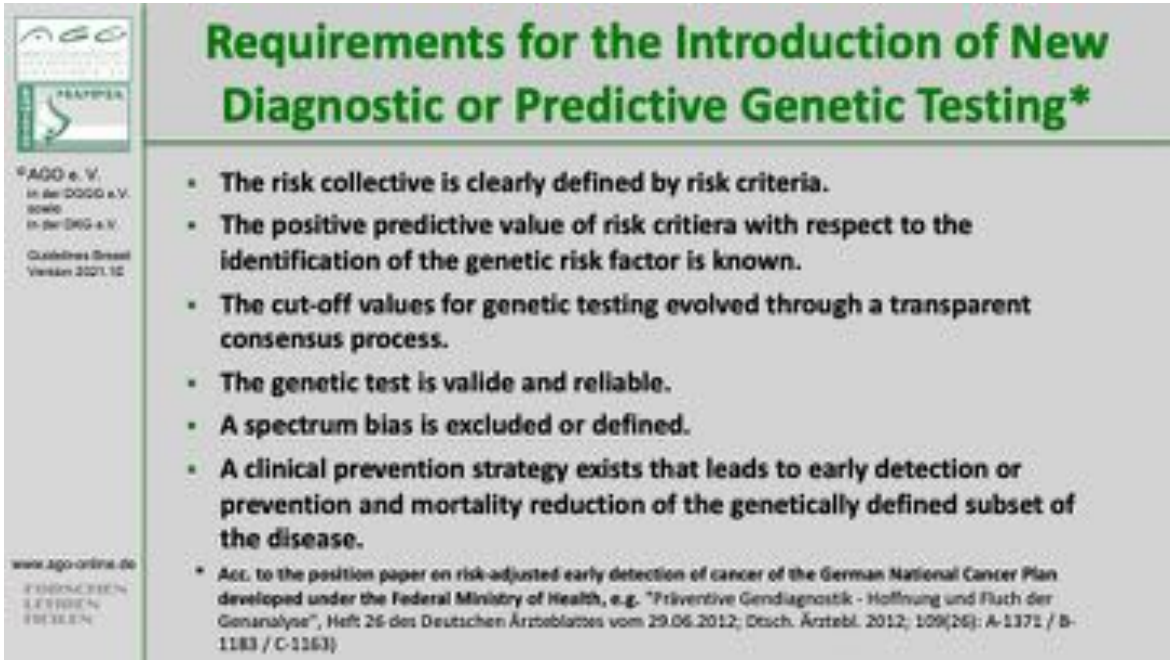
Proposed Classification System for Sequence Variants Identified by Genetic Testing		
Class	**Discription**	**Probabilty of being pathogenic**
5	Definitly pathogenic	> 0,99
4	Likely pathogenic	0,95 – 0,99
3	Uncertain	0,05 – 0,949
2	Likely not pathogenic or of little clinical significance	0,001 – 0,049
1	Not pathogenic or of no clinical significance	< 0,001

Only class 4 and 5 variants are considered clinically relevant.

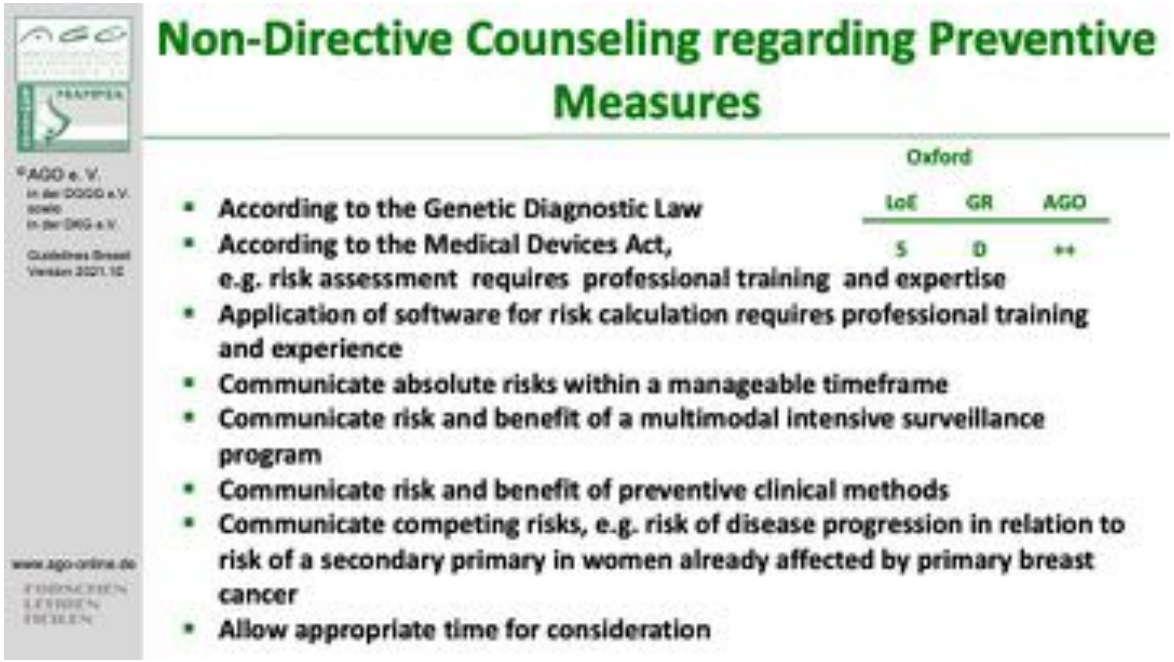
1. Plon SE, Eccles DM, Easton D, et al. Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. Human mutation. 2008;29(11):1282-91.



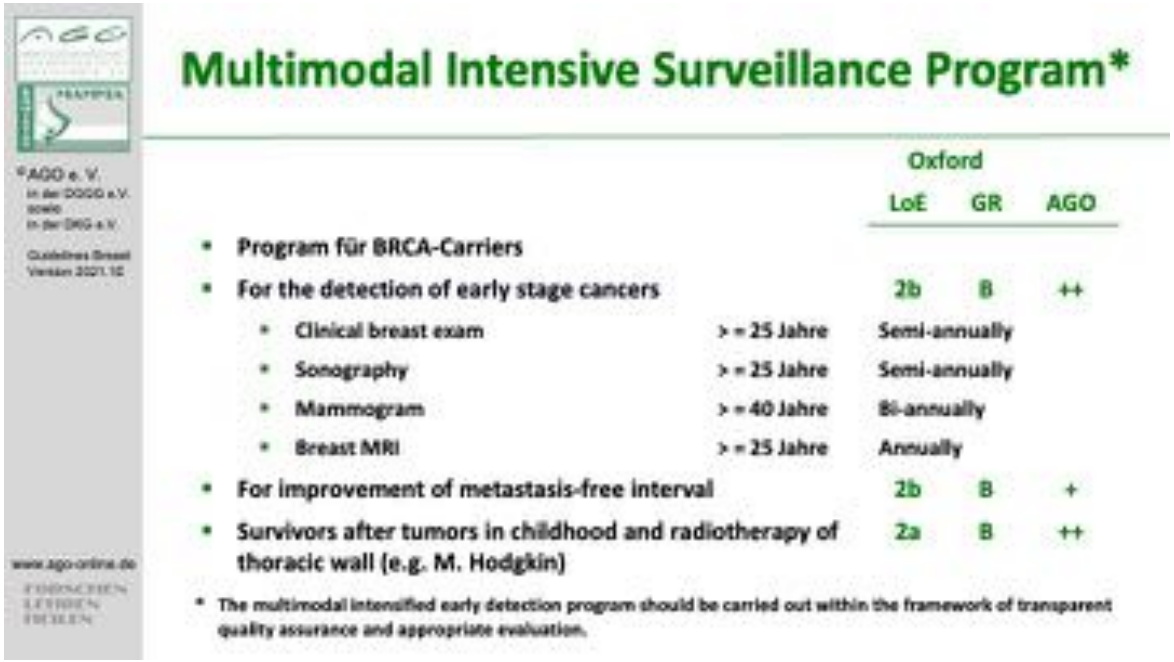
1. Spurdle AB, Healey S, Devereau A, et al. ENIGMA--evidence-based network for the interpretation of germline mutant alleles: an international initiative to evaluate risk and clinical significance associated with sequence variation in BRCA1 and BRCA2 genes. Human mutation. 2012;33(1):2-7.



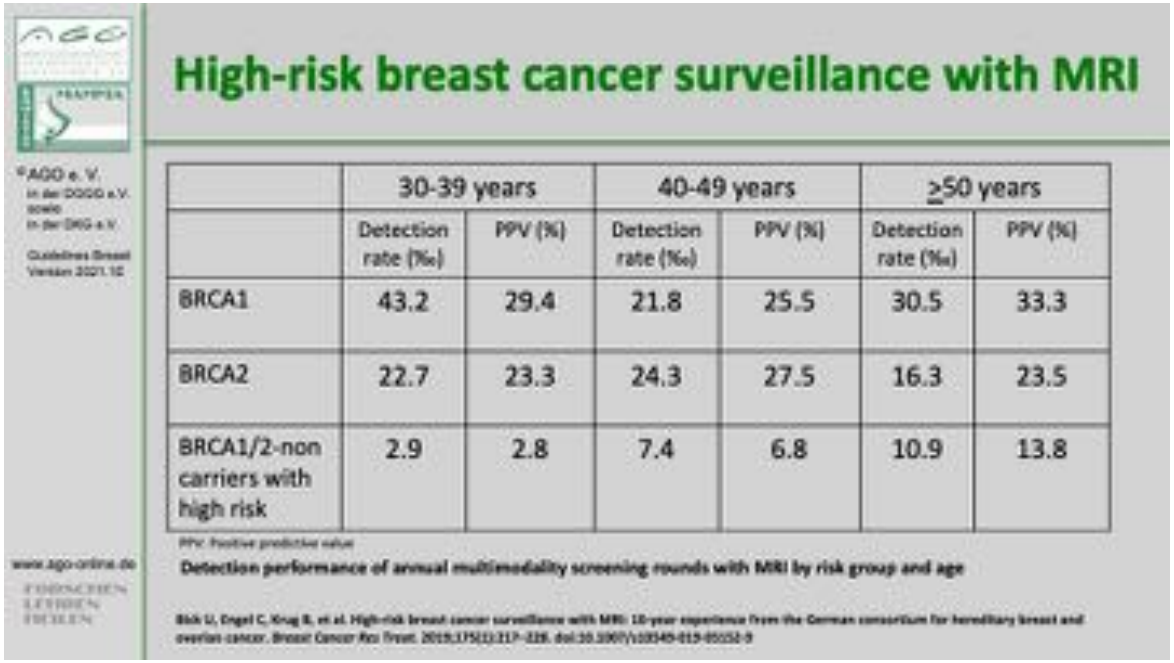
1. Schmutzler RK, et al. Risikoadaptierte Früherkennung, Ein Papier der Unterarbeitsgruppe „Risikoadaptierte Früherkennung der AG1 „Weiterentwicklung der Krebsfrüherkennung“ des Nationalen Krebsplans. http://wwwbmgbundde/fileadmin/dateien/Downloads/N/Nationaler_Krebsplan/Zielepapier_zum_Querschnittsthema_Risiko-adaptierte_Krebsfrueherkennung.pdf. 2011.
2. "Präventive Gendiagnostik - Hoffnung und Fluch der Genanalyse", Heft 26 des Deutschen Ärzteblattes vom 29.06.2012; Dtsch. Ärztebl. 2012; 109(26): A-1371 / B-1183 / C-1163),



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



1. Albert US, Schreer I; Arbeitsgruppe der Stufe-3-Leitlinie Mammarkarzinom. S3 guideline breast cancer: update on early detection, and mammography screening. Radiologe. 2019 Jan;59(1):13-18. doi: 10.1007/s00117-018-0473-6.
2. 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
3. Ellen Warner: Screening BRCA1 and BRCA2 Mutation Carriers for Breast Cancer. Review. Cancers 2018, 10, 477; doi:10.3390/cancers10120477
4. Evans, D.G.; Kesavan, N.; Lim, Y. et al.: MRI breast screening in high-risk women: Cancer detection and survival analysis. Breast Cancer Res. Treat. 2014, 145: 663–672
5. Leach MO, Boggis CR, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet. 2005;365(9473):1769-78.
6. Meindl A, Ditsch N, Kast K, et al. Hereditary breast and ovarian cancer: new genes, new treatments, new concepts. Dtsch Arztebl Int. 2011;108(19):323-30.

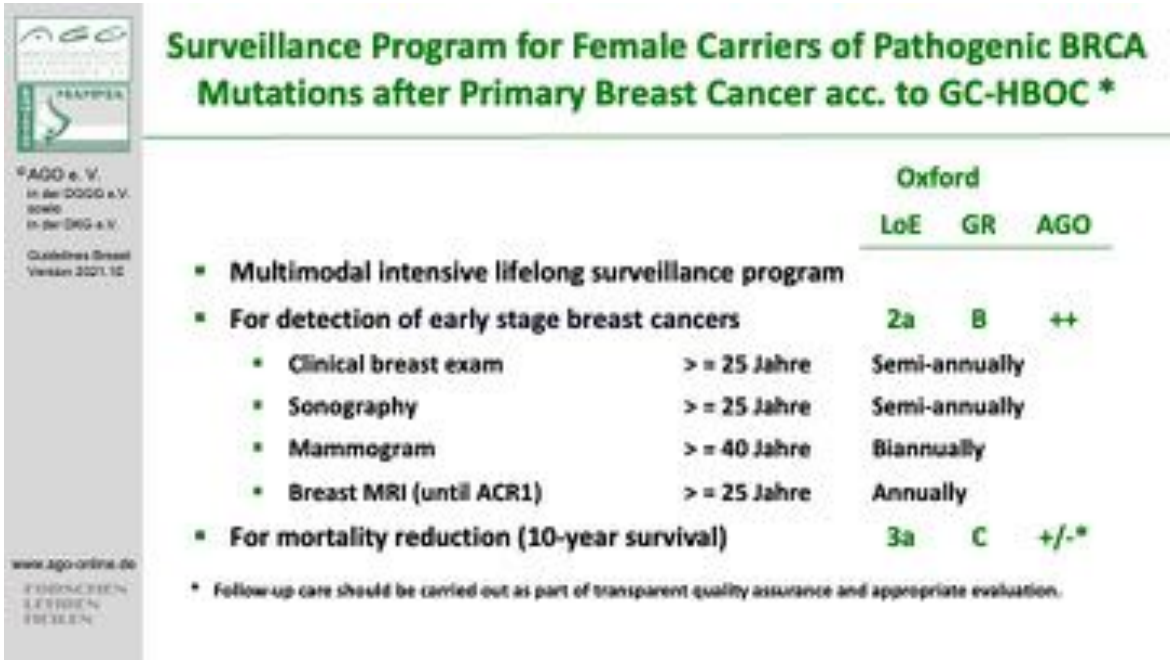


	30-39 years		40-49 years		≥50 years	
	Detection rate (‰)	PPV (%)	Detection rate (‰)	PPV (%)	Detection rate (‰)	PPV (%)
BRCA1	43.2	29.4	21.8	25.5	30.5	33.3
BRCA2	22.7	23.3	24.3	27.5	16.3	23.5
BRCA1/2-non carriers with high risk	2.9	2.8	7.4	6.8	10.9	13.8

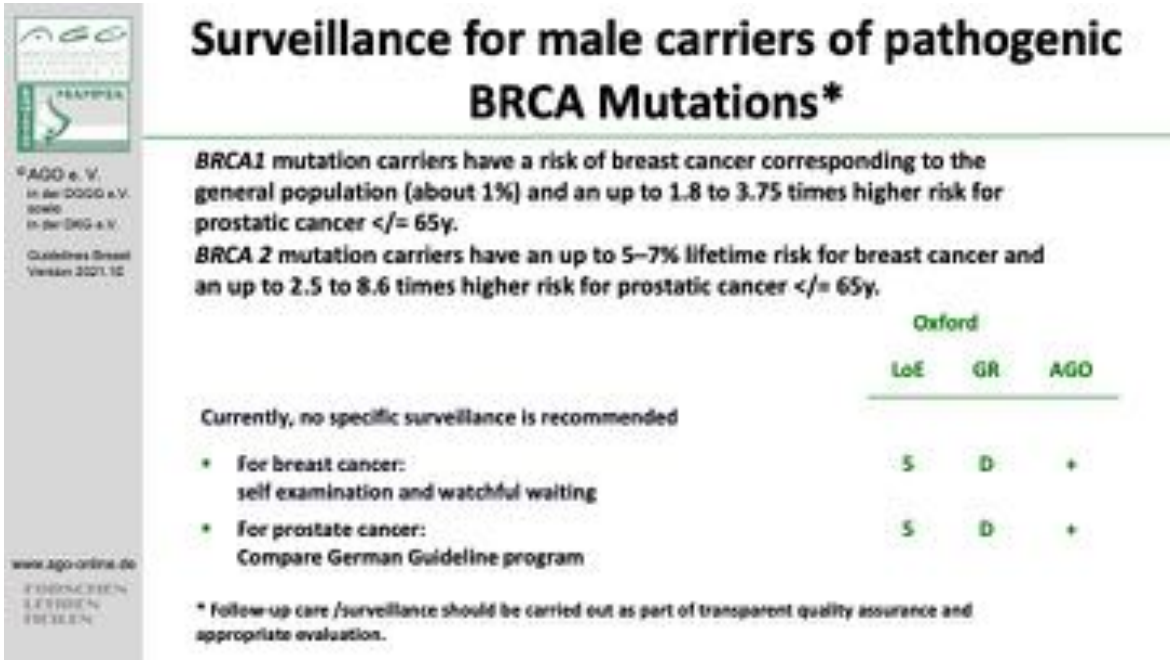
PPV: Positive predictive value

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

1. Bick U, Engel C, Krug B et al.: German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC). 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 May;175(1):217-228. doi: 10.1007/s10549-019-05152-9. Epub 2019 Feb 6. PMID: 30725383.

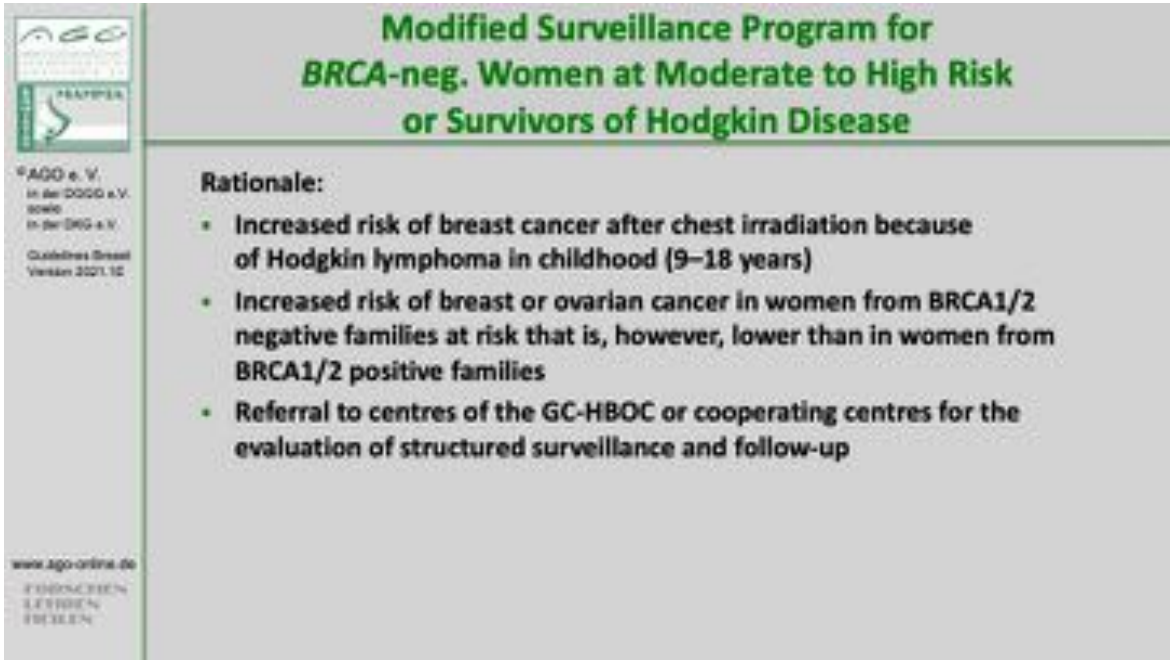


1. Albert US, Schreer I; Arbeitsgruppe der Stufe-3-Leitlinie Mammarkarzinom. S3 guideline breast cancer: update on early detection, and mammography screening. Radiologe. 2019 Jan;59(1):13-18. doi: 10.1007/s00117-018-0473-6.
2. Bick U, Engel C, Krug B et al.: German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC). 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 May;175(1):217-228. doi: 10.1007/s10549-019-05152-9. Epub 2019 Feb 6. PMID: 30725383.
3. Carbine NE, Lostumbo L, Wallace J et al.: Risk-reducing mastectomy for the prevention of primary breast cancer. Cochrane Database Syst Rev. 2018 Apr 5;4:CD002748. Review
4. Leach MO, Boggis CR, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet. 2005;365(9473):1769-78.
5. Meindl A, Ditsch N, Kast K, et al. Hereditary breast and ovarian cancer: new genes, new treatments, new concepts. Dtsch Arztebl Int. 2011;108(19):323-30.
6. Yao K et al.: Contralateral prophylactic mastectomy: current perspectives: Int J Womens Health 2016, 8:213-23. doi: 10.2147/IJWH.S82816

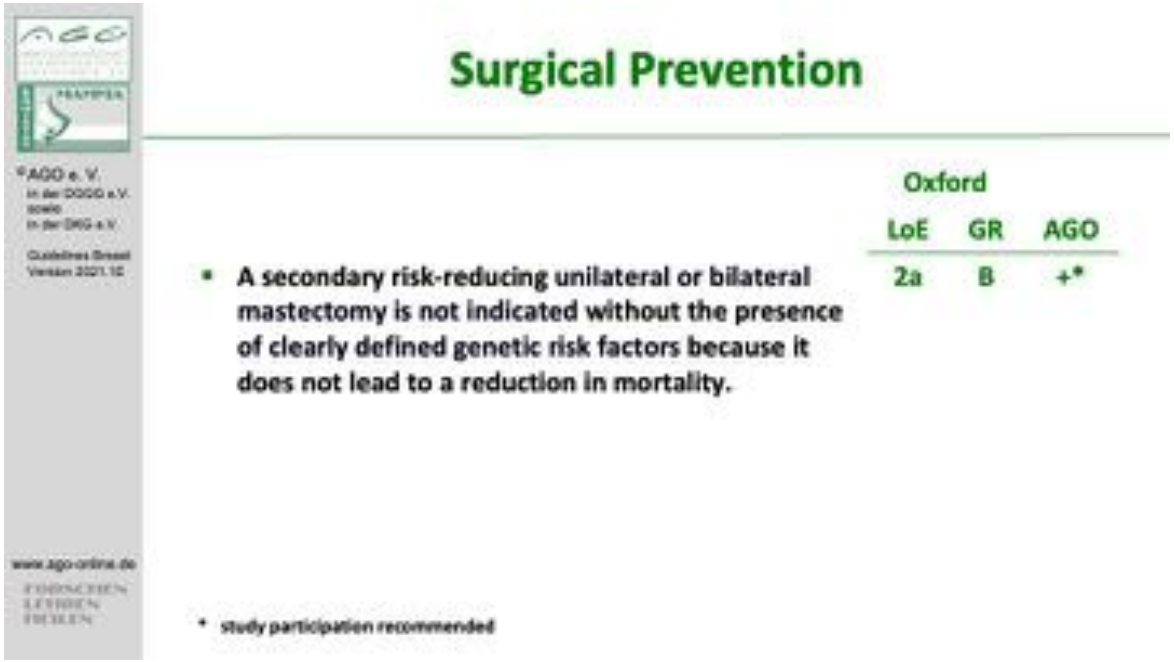


1. Albert US, Schreer I; Arbeitsgruppe der Stufe-3-Leitlinie Mammarkarzinom. S3 guideline breast cancer: update on early detection, and mammography screening. Radiologe. 2019 Jan;59(1):13-18. doi: 10.1007/s00117-018-0473-6.
2. van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, et al. Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet. 2005;42(9):711-9.
3. Bancroft EK, Page EC, Castro E, et al. Targeted prostate cancer screening in BRCA1 and BRCA2 mutation carriers: results from the initial screening round of the IMPACT study. Eur Urol. 2014;66(3):489-99.
4. Bancroft EK, Eeles RA, authors. Corrigendum to "Targeted Prostate Cancer Screening in BRCA1 and BRCA2 Mutation Carriers: Results from the Initial Screening Round of the IMPACT Study" [Eur Urol 2014;66:489-99]. Eur Urol. 2015;67(6):e126.
5. Giri VN et al. Philadelphia Prostate Cancer Consensus Conference 2019. J Clin Oncol 38:2798-2811.
6. Kote-Jarai Z, Leongamornlert D, Saunders E, et al. BRCA2 is a moderate penetrance gene contributing to young-onset prostate cancer: implications for genetic testing in prostate cancer patients. Br J Cancer. 2011;105(8):1230-4.
7. Leongamornlert D, Mahmud N, Tymrakiewicz M, et al. Germline BRCA1 mutations increase prostate cancer risk. Br J Cancer. 2012;106(10):1697-701.
8. Mikropoulos C, Selkirk CGH, Saya S, et al. Prostate-specific antigen velocity in a prospective prostate cancer screening study of men with genetic predisposition. Br J Cancer. 2018 Jan;118(2):266-276. doi: 10.1038/bjc.2017.429. Epub 2018 Jan 4. Erratum in: Br J Cancer. 2018 Mar 06.

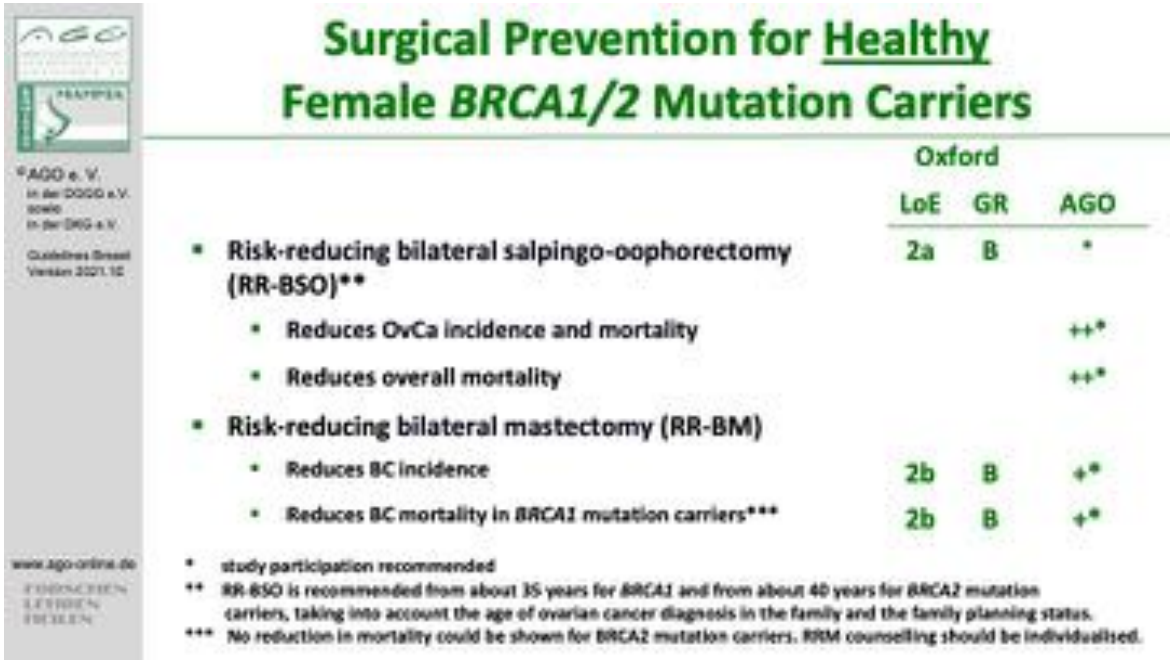
9. Page EC, Bancroft EK, Brook MN, et al. Interim Results from the IMPACT Study: Evidence for Prostate-specific Antigen Screening in BRCA2 Mutation Carriers. *Eur Urol*. 2019;76(6):831–842. doi:10.1016/j.eururo.2019.08.019
10. S3-Leitlinie Prostatakarzinom (Version 5.1, 2019)



1. Darrington DL, Vose JM. Appropriate surveillance for late complications in patients in remission from Hodgkin lymphoma. Curr Hematol Malig Rep. 2012;7(3):200-7.
2. Ibrahim EM, Abouelkhair KM, Kazkaz GA, et al. Risk of second breast cancer in female Hodgkin's lymphoma survivors: a meta-analysis. BMC Cancer. 2012;12:197.
3. Meindl A, Ditsch N, Kast K, et al. Hereditary breast and ovarian cancer: new genes, new treatments, new concepts. Dtsch Arztebl Int. 2011;108(19):323-30.
4. Veit-Rubin N, Rapiti E, Usel M, et al. Risk, characteristics, and prognosis of breast cancer after Hodgkin's lymphoma. Oncologist. 2012;17(6):783-91.
5. Schellong G, Riepenhausen M, Ehlert K, et al. Breast cancer in young women after treatment for Hodgkin's disease during childhood or adolescence--an observational study with up to 33-year follow-up. *Dtsch Arztebl Int*. 2014;111(1-2):3-9. doi:10.3238/arztebl.2014.0003
6. Schmutzler RK, Rhiem K, Bick U; German Consortium for Hereditary Breast and Ovarian Cancer. Breast cancer in young women after treatment for Hodgkin's disease during childhood or adolescence--an observational study with up to 33-year follow-up. Dtsch Arztebl Int. 2014 Jan 6;111(1-2):3-9. doi: 10.3238/arztebl.2014.0003. PMID: 24565270; PMCID: PMC3948013.



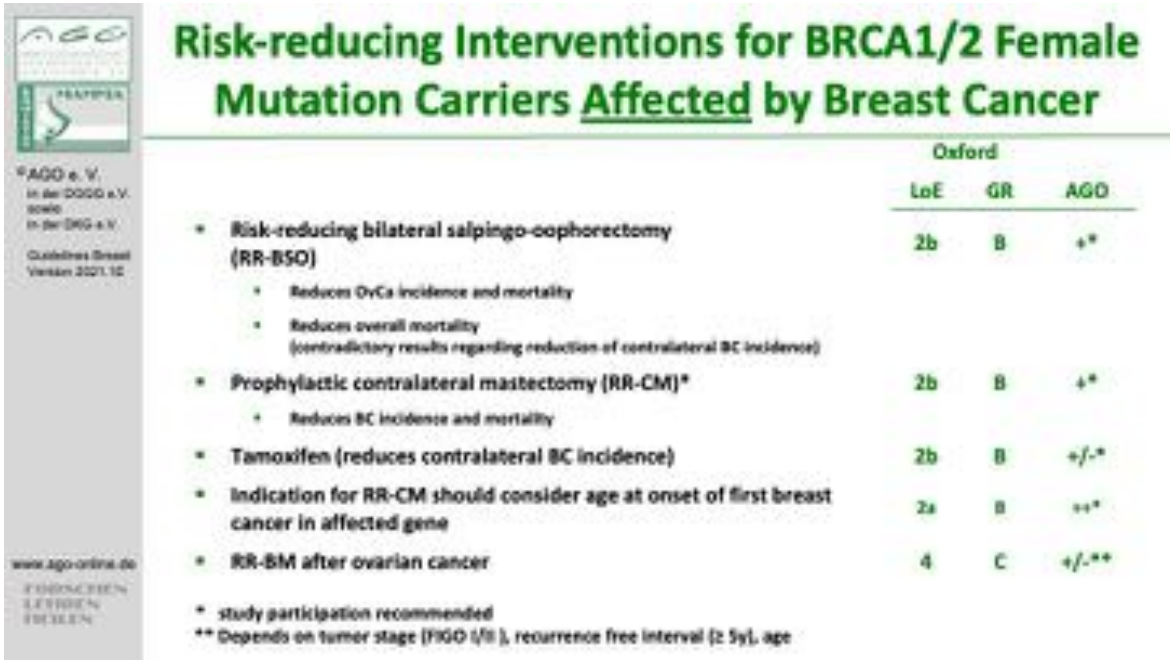
1. Kurian AW, Lichtensztajn DY, Keegan TH, et al. Use of and mortality after bilateral mastectomy compared with other surgical treatments for breast cancer in California, 1998-2011. JAMA. 2014;312(9):902-14.
2. Copson ER, Maishman TC, Tapper WJ, et al: Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. Lancet Oncol 2018, DOI: http://dx.doi.org/10.1016/S1470-2045(17)30891-4.



1. Domchek SM, Friebel TM, Neuhausen SL, et al. Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. Lancet Oncol. 2006;7(3):223-9.
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.
3. Heemskerk-Gerritsen BAM, Seynaeve C, van Asperen CJ, et al.: Breast Cancer Risk After Salpingo-Oophorectomy in Healthy BRCA1/2 Mutation Carriers: Revisiting the Evidence for Risk Reduction. JNCI J Natl Cancer Inst (2015) 107(5): djv033
4. Heemskerk-Gerritsen BAM, Jager A, Koppert LB et al: Survival after bilateral risk-reducing mastectomy in healthy BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat 2019, 177(3):723-733.
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.
6. Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2002;346(21):1609-15.
7. Kotsopoulos J, Huzarski T, Gronwald J, et al: Hereditary Breast Cancer Clinical Study Group. Bilateral Oophorectomy and Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers. J Natl Cancer Inst. 2016 Sep 6;109(1). doi: 10.1093/jnci/djw177. Print 2017 Jan.
8. Lostumbo L, Carbine NE, Wallace J. Prophylactic mastectomy for the prevention of breast cancer. Cochrane Database Syst Rev.

2010(11):CD002748.

9. Mavaddat N, Antoniou AC, Mooij TM et al: Risk-reducing salpingo-oophorectomy, natural menopause, and breast cancer risk: an international prospective cohort of BRCA1 and BRCA2 mutation carriers. Breast Cancer Res 2020, 22(1):8.
10. Meijers-Heijboer H, van Geel B, van Putten WL, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2001;345(3):159-64.
11. Rebbeck TR, Friebel T, Lynch HAT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol. 2004;22(6):1055-62.
12. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med. 2002;346(21):1616-22.
13. Xiao YL, Wang K, Liu Q, Li J, Zhang X, Li HY. Risk Reduction and Survival Benefit of Risk-Reducing Salpingo-oophorectomy in Hereditary Breast Cancer: Meta-analysis and Systematic Review. Clin Breast Cancer. 2019 Feb;19(1):e48-e65. doi: 10.1016/j.clbc.2018.09.011. Epub 2018 Oct 4. PMID: 30470623.



1. Domchek SM, Jhaveri K, Patil S et al. Risk of metachronous breast cancer after BRCA mutation associated ovarian cancer. Cancer 2013;119:1344-8.
2. Evans DG, Ingham SL, Baildam A, et al. Contralateral mastectomy improves survival in women with BRCA1/2-associated breast cancer. Breast Cancer Res Treat. 2013;140(1):135-42.
3. Fong A, Cass I, John C, Gillen J, Moore KM, Gangi A, Walsh C, Li AJ, Rimel BJ, Karlan BY, Amersi F. Breast Cancer Surveillance Following Ovarian Cancer in BRCA Mutation Carriers. Am Surg. 2020 Oct;86(10):1243-1247. doi: 10.1177/0003134820964208. Epub 2020 Oct 26. PMID: 33106023.
4. Graeser MK, Engel C, Rhiem K, et al. Contralateral breast cancer risk in BRCA1 and BRCA2 mutation carriers. J Clin Oncol. 2009;27(35):5887-92.
5. Heemskerk-Gerritsen BA, Rookus MA, Aalfs CM, et al. Improved overall survival after contralateral risk-reducing mastectomy in BRCA1/2 mutation carriers with a history of unilateral breast cancer: a prospective analysis. Int J Cancer. 2015;136(3):668-77.
6. Jacobson M, Narod SA: Does oophorectomy reduce breast cancer mortality for BRCA mutation carriers after breast cancer? Expert Rev Anticancer Ther. 2018 Apr;18(4):305-306
7. Kotsopoulos J, Narod SA Prophylactic mastectomy for BRCA mutation carriers after ovarian cancer treatment: is it beneficial? Expert Rev Anticancer ,18(3):199-200.

8. McGee J, Giannakeas V, Karlan B, et al. Risk of breast cancer after a diagnosis of ovarian cancer in BRCA mutation carriers: is preventive mastectomy warranted? Gynecol Oncol. 2017 May;145(2):346–351.
9. Metcalfe K, Gershman S, Ghadirian P, et al. Contralateral mastectomy and survival after breast cancer in carriers of BRCA1 and BRCA2 mutations: retrospective analysis. BMJ. 2014;348:g226.
10. Metcalfe K, Lynch HT, Foulkes WD, et al. Effect of Oophorectomy on Survival After Breast Cancer in BRCA1 and BRCA2 Mutation Carriers. JAMA Oncol. 2015;1(3):306-13.
11. Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol. 2004;22(12):2328-35.
12. Metcalfe KA, Lubinski J, Ghadirian P, et al. Predictors of contralateral prophylactic mastectomy in women with a BRCA1 or BRCA2 mutation: the Hereditary Breast Cancer Clinical Study Group. J Clin Oncol. 2008;26(7):1093-7.
13. Phillips KA, Milne RL, Rookus MA et al. Tamoxifen and risk of contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. J Clin Oncol 2013,31(25):3091-9.
14. Rhiem K, Engel C, Graeser M, et al. The risk of contralateral breast cancer in patients from BRCA1/2 negative high risk families as compared to patients from BRCA1 or BRCA2 positive families: a retrospective cohort study. Breast Cancer Res. 2012;14(6):R156.
15. Ye-Lei Xiao, Kang Wang, Qiang Liu, et al.: Risk Reduction and Survival Benefit of Risk-Reducing Salpingo-oophorectomy in Hereditary Breast Cancer: Meta-analysis and Systematic Review. Clinical Breast Cancer, Vol. 19, No. 1, e48-65

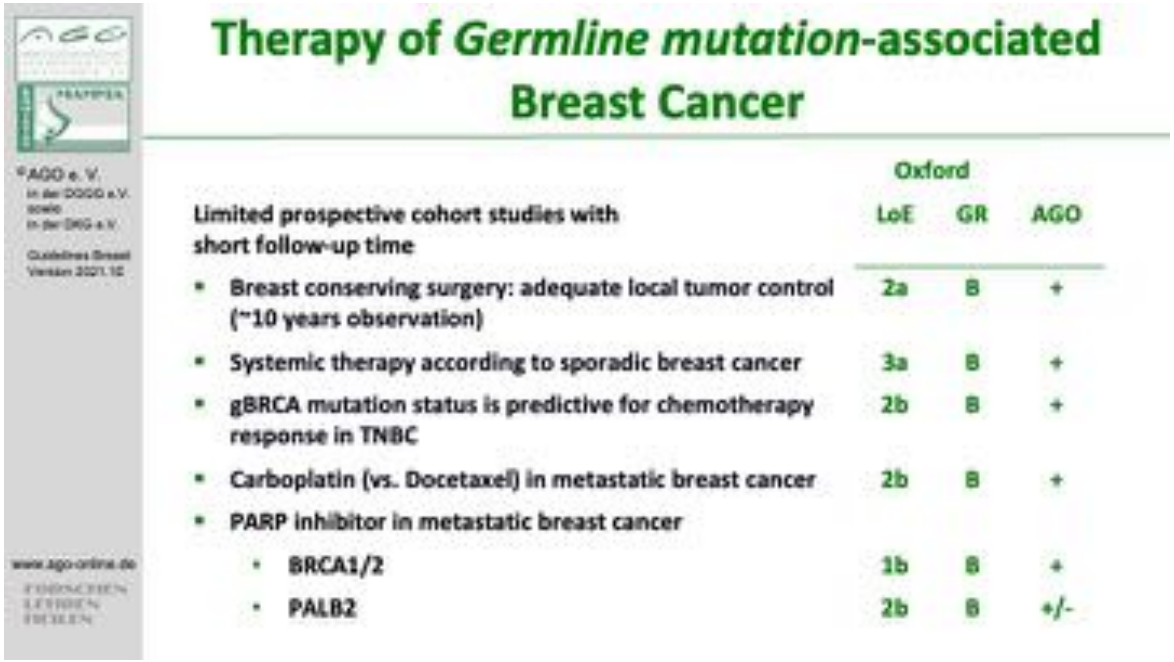
Improved Overall Survival After Contralateral Risk-reducing Mastectomy in *BRCA1/2* Mutation Carriers with a history of unilateral breast cancer: a prospective analysis.

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.

1. Heemskerk-Gerritsen BA, Rookus MA, Aalfs CM, et al. Improved overall survival after contralateral risk-reducing mastectomy in BRCA1/2 mutation carriers with a history of unilateral breast cancer: a prospective analysis. Int J Cancer. 2015;136(3):668-77.



Breast-conserving therapy in BRCA1/2 mutation carriers

1. Co M, Liu T, Leung J et al. Breast Conserving Surgery for BRCA Mutation Carriers-A Systematic Review. Clin Breast Cancer. 2020 Jun;20(3):e244-e250. doi: 10.1016/j.clbc.2019.07.014. Epub 2019 Aug 22. PMID: 32144082.
2. Golshan M, Loibl S, Wong SM, et al. Breast Conservation After Neoadjuvant Chemotherapy for Triple-Negative Breast Cancer: Surgical Results From the BrighTNess Randomized Clinical Trial. JAMA Surg. 2020 Mar 1;155(3):e195410. doi: 10.1001/jamasurg.2019.5410. Epub 2020 Mar 18. PMID: 31913413; PMCID: PMC6990971.
3. Hallam S, Govindarajulu S, Huckett B, et al. BRCA1/2 Mutation-associated Breast Cancer, Wide Local Excision and Radiotherapy or Unilateral Mastectomy: A Systematic Review. Clin Oncol (R Coll Radiol). 2015;27(9):527-35.
4. Huang X, Cai XY, Liu JQ, et al. Breast-conserving therapy is safe both within *BRCA1/2* mutation carriers and noncarriers with breast cancer in the Chinese population. Gland Surg. 2020 Jun;9(3):775-787. doi: 10.21037/gs-20-531. PMID: 32775268; PMCID: PMC7347799.
5. Pierce LJ, Levin AM, Rebbeck TR, et al. Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. J Clin Oncol. 2006;24(16):2437-43.
6. Pogoda K, Niwińska A, Sarnowska E, et al. Effects of *BRCA* Germline Mutations on Triple-Negative Breast Cancer Prognosis. *J Oncol*. 2020;2020:8545643. Published 2020 Jan 27. doi:10.1155/2020/8545643

7. Ye F, Huang L, Lang G, et al. Cancer Med. 2020 Mar;9(5):1903-1910. doi: 10.1002/cam4.2836. Epub 2020 Jan 7. PMID: 31912664; PMCID: PMC7050073.
8. Yoon KH, Chae S, Kang E, et al. Contralateral Breast Cancer and Ipsilateral Breast Tumor Recurrence in *BRCA1/2* Carriers and Non-Carriers at High-Risk of Hereditary Breast Cancer. J Breast Cancer. 2019 Sep 30;22(4):587-598. doi: 10.4048/jbc.2019.22.e47. PMID: 31897332; PMCID: PMC6933036.

Response to chemotherapy:

1. Copson ER, Maishman TC, Tapper WJ, et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. Lancet Oncol. 2018 Feb;19(2):169-180. doi: 10.1016/S1470-2045(17)30891-4. Epub 2018 Jan 11. PMID: 29337092; PMCID: PMC5805863.
2. Fasching PA, Loibl S, Hu C et al. BRCA1/2 Mutations and Bevacizumab in the Neoadjuvant Treatment of Breast Cancer: Response and Prognosis Results in Patients With Triple-Negative Breast Cancer From the GeparQuinto Study. J Clin Oncol. 2018 Aug 1;36(22):2281-2287. doi: 10.1200/JCO.2017.77.2285. Epub 2018 May 23. PMID: 29791287; PMCID: PMC6067803.
3. Hahnen E, Lederer B, Hauke J et al: Germline Mutation Status, Pathological Complete Response, and Disease-Free Survival in Triple-Negative Breast Cancer: Secondary Analysis of the GeparSixto Randomized Clinical Trial. JAMA Oncol 2017, 3(10):1378-1385.
4. Loibl S, Weber KE, Timms KM et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response-final results from GeparSixto. Ann Oncol. 2018 Dec 1;29(12):2341-2347. doi: 10.1093/annonc/mdy460. PMID: 30335131.
5. Meisner E, Rollins R, Ensor J et al.: Efficacy of olaparib monotherapy in patients (pts) with HER2-negative metastatic breast cancer (MBC) with germline BRCA mutation (gBRCAm) or lesional BRCA mutation (lBRCAm). J Clin Oncol 2018, 36 (suppl; abstr 1074)

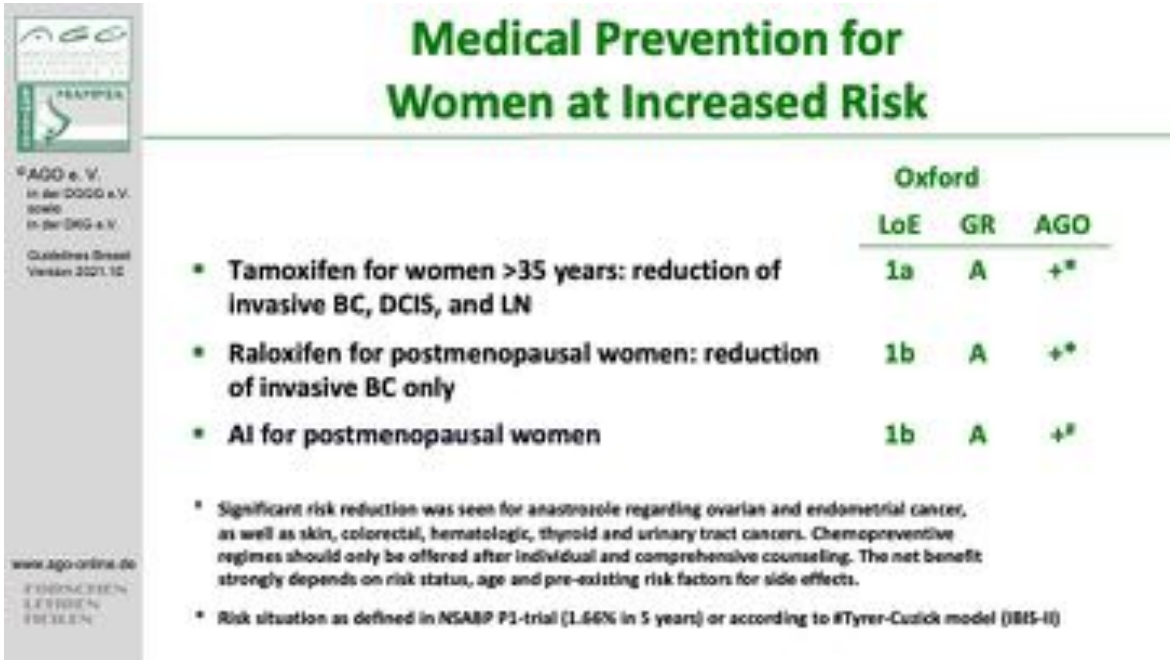
Carboplatin**:**

1. Somlo G, Frankel PH, Arun BK, et al: Efficacy of the PARP Inhibitor Veliparib with Carboplatin or as a Single Agent in Patients with Germline BRCA1- or BRCA2-Associated Metastatic Breast Cancer: California Cancer Consortium Trial NCT01149083. Clin Cancer Res. 2017 Mar 29. doi: 10.1158/1078-0432.CCR-16-2714
2. Tutt A, Tovey H, Cheang MCU, Kernaghan S et al.: Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness

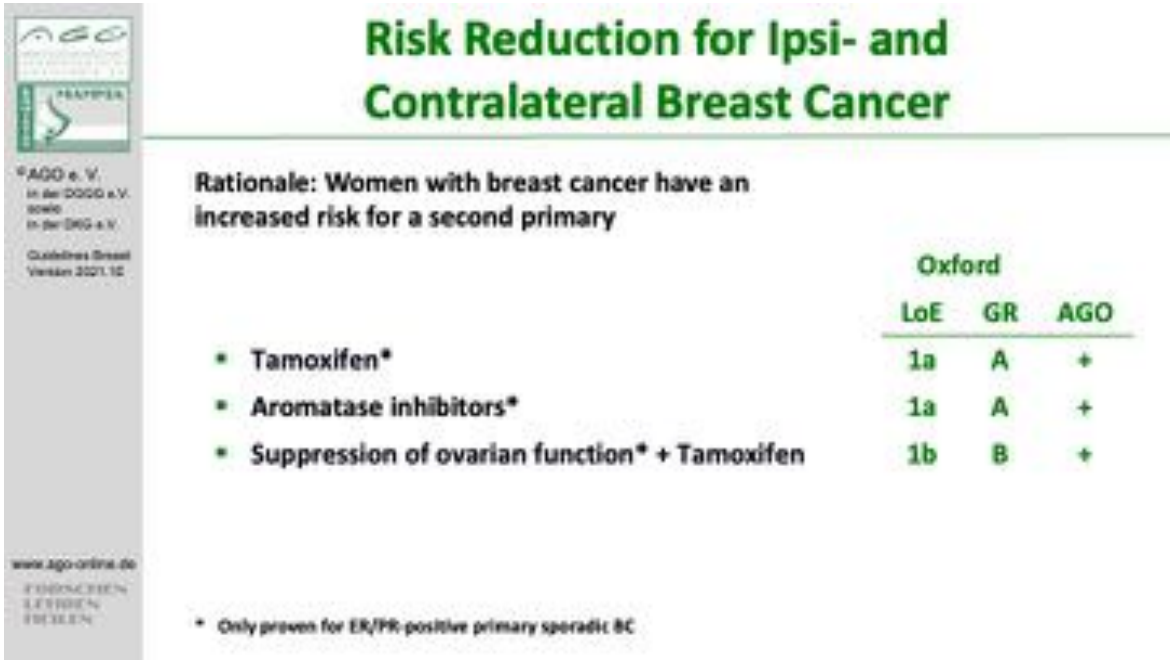
subgroups: the TNT Trial. Nat Med. 2018 May;24(5):628-637. doi: 10.1038/s41591-018-0009-7. Epub 2018 Apr 30.

PARPi:

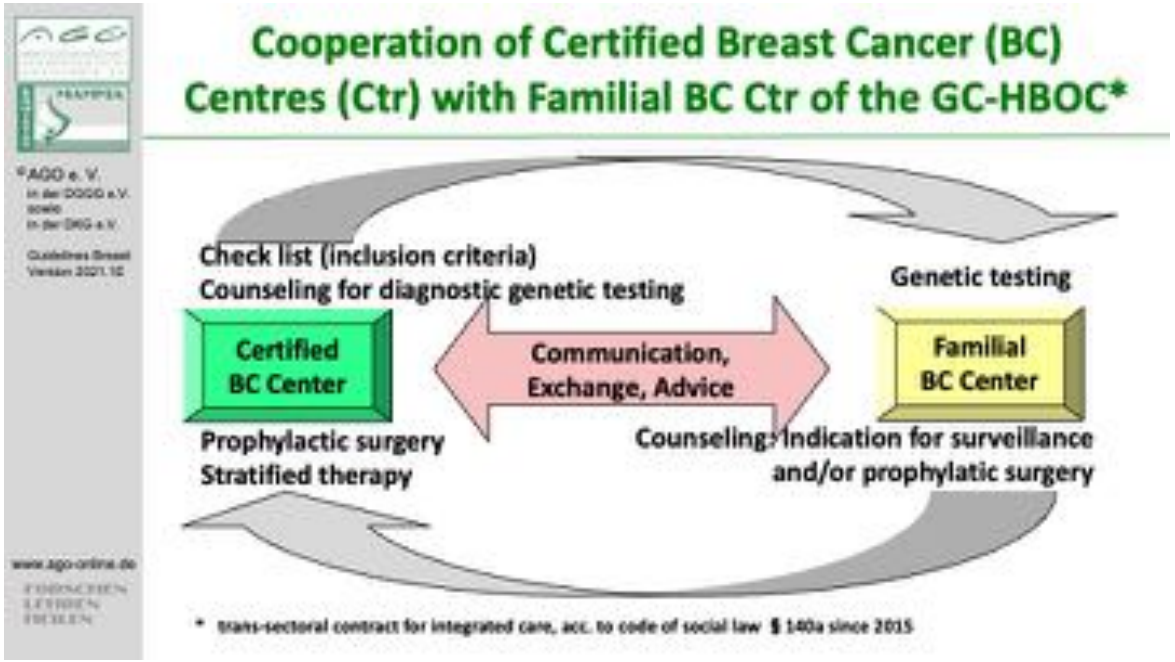
1. Ettl J, Quek RGW, Lee KH, et al. Quality of life with talazoparib versus physician's choice of chemotherapy in patients with advanced breast cancer and germline BRCA1/2 mutation: patient-reported outcomes from the EMBRACA phase III trial. Ann Oncol. 2018;29(9):1939–1947. doi:10.1093/annonc/mdy257
2. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med. 2018;379(8):753–763. doi:10.1056/NEJMoa1802905
3. Litton JK, Hurvitz SA, Mina LA, et al. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. Ann Oncol. 2020 Nov;31(11):1526-1535. doi: 10.1016/j.annonc.2020.08.2098. Epub 2020 Aug 20. PMID: 32828825.
4. Poggio F, Bruzzone M, Ceppi M et al.: Single-agent PARP inhibitors for the treatment of patients with BRCA-mutated Her2-negative metastatic breast cancer: a systematic review and meta-analysis. ESMO Open 2018, 3:e000361
5. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation [published correction appears in N Engl J Med. 2017 Oct 26;377(17):1700]. N Engl J Med. 2017;377(6):523–533.
6. Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol. 2019;30(4):558–566. doi:10.1093/annonc/mdz012
7. Robson M, Ruddy KJ, Im SA, et al. Patient-reported outcomes in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer receiving olaparib versus chemotherapy in the OlympiAD trial. Eur J Cancer. 2019 Oct;120:20-30. doi: 10.1016/j.ejca.2019.06.023.
8. Tung NM, Robson ME, Ventz S et al. TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes. J Clin Oncol. 2020 Dec 20;38(36):4274-4282. doi: 10.1200/JCO.20.02151. Epub 2020 Oct 29. PMID: 33119476.



1. Cuzick J, Sestak I, Cawthorn S, et al. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. Lancet Oncol. 2015;16(1):67-75.
2. Cuzick J, Sestak I, Forbes JF, et al. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial. Lancet. 2020;395(10218):117–122. doi:10.1016/S0140-6736(19)32955-1
3. Forbes JF, Sestak I, Howell A, et al. Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial. Lancet. 2016;387(10021):866-73.
4. Goss PE, Ingle JN, Ales-Martinez JE, et al. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med. 2011;364(25):2381-91.
5. King MC, Wieand S, Hale K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA. 2001;286(18):2251-6.
6. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA. 2006;295(23):2727-41.



1. Breast International Group 1-98 Collaborative Group, Thurlimann B, Keshaviah A, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med. 2005;353(26):2747-57.
2. Early Breast Cancer Trialists' Collaborative G. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365(9472):1687-717.
3. Early Breast Cancer Trialists' Collaborative G, Dowsett M, Forbes JF, et al. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015;386(10001):1341-52.


Cooperation of Certified Breast Cancer (BC) Centres (Ctr) with Familial BC Ctr of the GC-HBOC*
AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.
Guidelines Breast
Version 2021.1E
Check list (inclusion criteria)
Counseling for diagnostic genetic testing
Genetic testing
Certified BC Center
Communication, Exchange, Advice
Familial BC Center
Prophylactic surgery
Stratified therapy
Counseling: Indication for surveillance and/or prophylatic surgery
www.ago-online.de
* trans-sectoral contract for integrated care, acc. to code of social law § 140a since 2015