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Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Breast Cancer Risk, Genetics and Prevention



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Breast Cancer Risk and Prevention

- **Versions 2003–2024:**

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Germline Testing – Therapeutic Consequences

Irrespective of family history

gBRCA1/2 pV
gPALB2 pV

	Oxford		
	LoE	GR	AGO
<i>1a</i>		A	++
<i>2b</i>		B	+

Therapy of likely pathogenic / pathogenic germline variants - Associated Breast Cancer

	Oxford		
	LoE	GR	AGO
▪ Breast conserving surgery according common standard (adequate local tumor control in long time follow up, IBTR RR 1,6, no worse overall survival, Follow-up ≥ 10 years observation)	2a	B	+
▪ Systemic therapy according to common standard	3a	B	+
▪ <i>gBRCA</i> pathogenic variants (pV) is predictive for neoadjuvant chemotherapy in early TNBC	2b	B	
▪ <i>gBRCA</i> pV is predictive for Carboplatin (vs. Docetaxel) in metastatic breast cancer	1b	B	
PARP inhibitor (Her2-negative carcinoma):			
▪ eBC high risk:			
▪ Olaparib (in case of <i>gBRCA1/2</i> pV)*	1b	A	++
▪ mBC:			
▪ Olaparib, Talazoparib in <i>gBRCA 1/2</i> pV	1b	A	++
▪ Olaparib in <i>sBRCA 1/2</i> pV (somatic mutation)	2b	B	+
▪ Olaparib in <i>gPALB2</i> pV	2b	B	+

eBC: Early Breast Cancer; mBC: Metastatic Breast Cancer; pV: likely pathogenic / pathogenic variant (class 4/5) = mutation; IBTR: ipsilateral breast tumor recurrence; * Use according to study inclusion criteria and approval

BCS bei BRCA 1/2 Mutationsträgern:

1. Nara M, Ishihara S, Kitano A, et al. Does breast-conserving surgery with radiotherapy in BRCA-mutation carriers significantly increase ipsilateral breast tumor recurrence? A systematic review and meta-analysis Breast Cancer 2022 May;29(3):394-401.doi: 10.1007/s12282-022-01343-3. Epub 2022 PMID: 35212965
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8. Hallam S, Govindarajulu S, Hockett 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.
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Chemotherapiesprechen:

1. Zheng F, Du F, Wang W et al. Updated efficacy of adjuvant epirubicin plus cyclophosphamide followed by taxanes versus carboplatin plus taxanes in early triple-negative breast cancer in phase 2 trial: 8.1-year median follow-up. *Breast Cancer Res Treat*. 2022 Jan;191(1):97-105.
2. 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.
3. 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.
4. 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.
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)
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Carboplatin eBC:

1. Caramelo O, Silva C, Caramelo F et al. Efficacy of different neoadjuvant treatment regimens in BRCA-mutated triple negative breast cancer: a systematic review and meta-analysis. *Hered Cancer Clin Pract*. 2022 Sep 9;20(1):34.
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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 Aug 1;23(15):4066-4076.
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PARP-inhibitors eBC high-risk:

1. Zambelli A, Cortesi L, Gaudio M, et al. Parp-inhibitors in the therapeutic landscape of breast cancer patients with BRCA1 and BRCA2 pathogenic germline variants: An Italian consensus paper and critical review Cancer Treat Rev. 2024 Nov;130:102815. doi: 10.1016/j.ctrv.2024.102815.
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PARP-inhibitors mBC:

1. Qureshi Z, Jamil A, Altaf F, Siddique R, Safi A. Efficacy and Safety of BRCA-targeted Therapy (Polyadenosine Diphosphate-ribose Polymerase Inhibitors) in Treatment of BRCA-mutated Breast Cancer: A Systematic Review and Meta-analysis. Am J Clin Oncol. 2024 Nov 1;47(11):555-562. doi: 10.1097/COC.0000000000001120
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negative metastatic breast cancer in a real-world setting: final analysis of LUCY. *Breast Cancer Res Treat.* 2024 Apr;204(2):237-248. doi:10.1007/s10549-023-07165-x.

3. Zambelli A, Cortesi L, Gaudio M, et al. Parp-inhibitors in the therapeutic landscape of breast cancer patients with BRCA1 and BRCA2 pathogenic germline variants: An Italian consensus paper and critical review *Cancer Treat Rev.* 2024 Nov;130:102815. doi: 10.1016/j.ctrv.2024.102815.
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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.
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9. 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.
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12. 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;377(17):1700]. *N Engl J Med.* 2017;377(6):523–533.

PARP-inhibitors mBC gPALB2mut:

1. 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.



Indication for Genetic testing of Index Patient in the *BRCA1/2* Genes and possibly other Risk Genes

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

If one of these criteria of the German Familial Breast and Ovarian Cancer Consortium (DK-FBREC) is present, the probability of detecting a probable pathogenic / pathogenic germline variant (pV) in the *BRCA1* and *BRCA2* mutation genes is $\geq 10\%$, EBM reimbursement guaranteed. Examination within and outside an DK-FBREC center possible for.

From one family branch at least*

- three women with breast cancer independent of age
- two women with breast cancer, one diagnosed before the 51st birthday
- one woman affected by breast and one by ovarian cancer or
- one woman affected by breast and ovarian cancer or
- two women affected by ovarian cancer or
- one woman affected by bilateral breast cancer, first before 51st birthday
- one woman affected by breast cancer before the 36th birthday or
- one man affected by breast cancer and one woman affected by breast or ovarian cancer

- All mutation carriers should be registered in scientific databases, to validate the inclusion and exclusion criteria (including population-based studies).

1. 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
2. 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.
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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5. Manchanda R, Gaba F. Population Based Testing for Primary Prevention: A Systematic Review. *Cancers (Basel).* 2018 Nov 5;10(11).
6. Rolfes M, Borde J, Möllenhoff K et al, Prevalence of Cancer Predisposition Germline Variants in Male Breast Cancer Patients: Results of the German Consortium for Hereditary Breast and Ovarian Cancer, *Cancers*, 2022, 14(13): 3292

Indication for Genetic Examination of Index Patient *BRCA1/2* Genes and Possibly Further Risk Genes

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

■ **For further recommended criteria:**

- one disease of triple negative breast cancer diagnosed before 70th birthday*
- one disease of ovarian cancer before 80th birthday*
- one man affected by breast cancer

a significance for at least a 10% probability of detecting likely pathogenic / pathogenic variants (pV) has not yet been conclusively established. Therefore, they must be further systematically validated.

* Cost coverage at the DK-FBREK centers

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
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. 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.
6. Manchanda R, Gaba F. Population Based Testing for Primary Prevention: A Systematic Review. *Cancers (Basel)*. 2018 Nov 5;10(11).
7. 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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9. Rhiem K, Zachariae S, Waha A, Grill S, Hester A, Golatta M, van Mackelenbergh M, Fehm T, Schläiß T, Ripperger T, Ledig S, Meisel C, Speiser D, Veselinovic K, Schröder C, Witzel I, Gallwas J, Weber BHF, Solbach C, Aktas B, Hahnen E, Engel C, Schmutzler R. Prevalence of Pathogenic Germline Variants in Women with Non-Familial Unilateral Triple-Negative Breast Cancer. *Breast Care (Basel)*. 2023 May;18(2):106-112. doi: 10.1159/000528972. Epub 2023 Jan 6. PMID: 37261134; PMCID: PMC10228253.

Extended Indication for Genetic Testing of the Genes *BRCA1*, *BRCA2*, *TP53*, *PALB2*, *CDH1*, *PTEN*, *STK11* and Further Risk Genes (according NCCN)

- Genetic Testing can be performed in patients with
 - Age at first diagnosis ≤ 65 years, irrespective of family history
 - Triple-negative histology and age at first diagnosis > 60 years, especially in families with further breast cancer cases (irrespective of age at diagnosis)
 - Invasive lobular histology and diffuse gastric cancer in the family history
 - In families with pancreatic cancer history and high risk prostate cancer history
 - Ashkenazi jews

These indications have not been validated with regard to their pV prevalence.

Cave: frequent VUS and decreased penetrance

1. Bedrosian I, Somerfield MR, Achatz MI, et al. Germline Testing in Patients With Breast Cancer: ASCO-Society of Surgical Oncology Guideline. J Clin Oncol. 2024 Feb 10;42(5):584-604. doi: 10.1200
2. NCCN Guideline 2024 https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

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	++

History and family history over at least three generation (including age of first disease)

- **Characteristic disease:**
 - Breast and ovarian cancer
- **Further disease:**
 - Pancreatic, thyroid, colorectal, stomache, hepatobiliar, 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.
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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. 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.
12. 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.
13. 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.
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.



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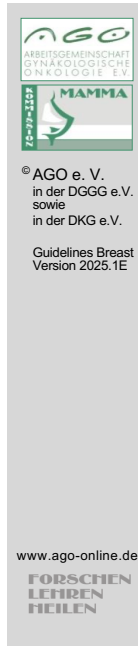
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Non BRCA-Associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer

Syndrom	Gene	Risk for malignancy
Li Fraumeni	<i>TP53</i>	Breast, endometrium, colorectal, small intestine, stomach, hepato biliary, skin, osteosarcoma, soft tissue sarcoma, urogenital, CNS, ACC, leukemia, lymphoma, lung
Cowden	<i>PTEN</i>	Breast, endometrium, thyroid, colorectal, kidney, melanoma
Hereditary diffuse gastric cancer syndrome	<i>CDH1</i>	Hereditary diffuse gastric cancer, lobular invasive breast cancer
Peutz-Jeghers Syndrome	<i>STK11/LKB1</i>	Colorectal, small intestine, stomach, pancreas, testicle, endometrium
Lynch	<i>MLH1, MSH2, MSH6, PMS2, EPCAM</i>	Endometrium, ovary, colorectal, small intestine, stomach, hepato biliary, pancreas, kidney, urogenital, CNS
Ataxia telangiectasia (AT-Syndrom)	<i>ATM</i>	Breast cancer, leukemia, stomach, melanoma, sarcoma
Fanconi Anämie	<i>BRCA2, BRIP1, RAD51C, PALB2</i>	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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12. 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.
13. 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.
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

- According to: **AGO ++**
 - The Genetic Diagnostic Law
 - The Medical Devices Act (e.g. risk assessment)
- Application of software for risk calculation requires professional training and experience (Software must be certified)
- Communication and consideration of:
 - 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

SOFTWARE (BOADICEA, IBIS):

1. Yang X, Mooij TM, Leslie G, et al. Validation of the BOADICEA model in a prospective cohort of BRCA1/2 pathogenic variant carriers. J Med Genet. 2024 Jul 19;61(8):803-809. doi: 10.1136/jmg-2024-109943. PMID: 38834293; PMCID: PMC11287562.

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Current Clinical Impact of Further Risk Genes and Variants

- Further moderate and low-risk gene variants are most likely transmitted in particular by an oligo- or polygenic trait.
- The penetrance of such genes is modified by own and family cancer history.
- Individual low-risk variants increase the risk of disease only insignificantly. They have a multiplicative effect, so that the analysis of multiple gene regions (polygenic risk score, PRS) will be of clinical relevance.

	Oxford		
	LoE	GR	AGO
Clinical genetic testing of moderate-risk genes, e.g. gene panels	1b	B	+*
Clinical genetic testing for low-risk variants (polygenic risk score, PRS)	2b	B	+*
Referral to specialised centers	5	D	+

* Currently, moderately penetrant genes and low-risk variants should only be examined in the context of prospective cohort studies, such as that of the German consortium, in order to assess the clinical benefit.

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Pathogenic Variants with Moderate to High Lifetime Risk for Breast Cancer

	Oxford		
	LoE	GR	AGO
Age-related risks for breast cancer			
▪ high: <i>BRCA1, BRCA2, PALB2</i>			
▪ high: <i>CDH1, PTEN, TP53; STK11</i>			
▪ moderate: <i>ATM, CHEK2</i>			
▪ moderate: <i>BARD1, RAD51C, RAD51D</i>			
Clinical benefit* of a genetic test			
▪ <i>BRCA1, BRCA2</i>	1b	A	+++
▪ <i>PALB2</i>	3a	B	++
▪ <i>CDH1, PTEN, TP53, STK11</i>	3b	B	++
▪ <i>ATM, BARD1, CHEK2, RAD51C, RAD51D</i>	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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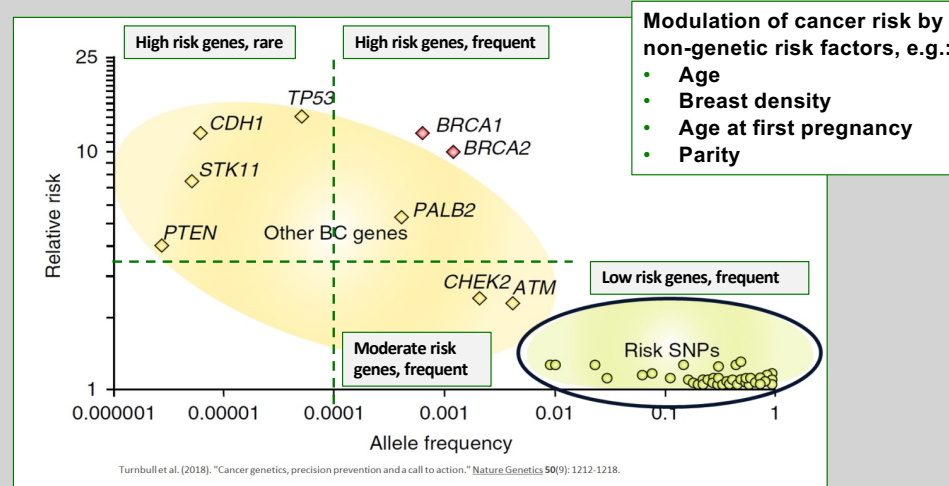
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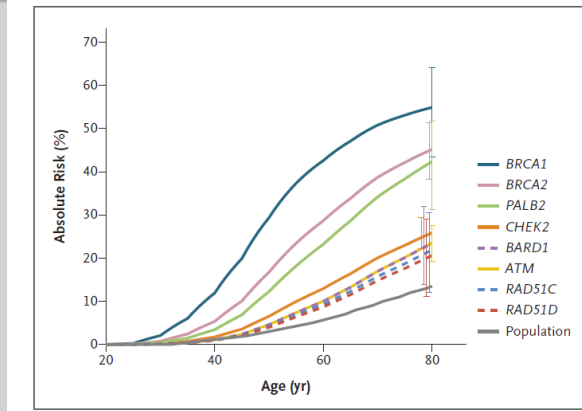
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Estimated Cumulative Risk of Breast Cancer with Protein-Truncating Variants in 8 Genes



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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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

1. 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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ACMG/AMP Variant Classification of Guidelines (Tavtigian SV et al., Human Mutation, 2020)

Class	Description	Probability of being pathogenic
5	Definitely 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 clinical significance	< 0.001

**Only class 4 and class 5 variants are considered clinically relevant.
Class 3 are considered as Variants of Unknown Significance (VUS).**

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Variant of Unknown Significance (VUS): Problems and Questions

- „A Variant of Unknown Significance (VUS) is a genetic variant with unknown clinical relevance.“ (Plon et al. Hum Mutat 2008)
- Most VUS are **extremely rare** (≤ 3 families in $> 80\%$ of variants)
- Classification of sequence variants should be performed according to ACMG/ClinGen and genspecific recommendations should be taken into account
- Frequency of VUS increases with numbers of tested genes
- In silico prediction tools alone are not adequate or sufficient for clinical decision making
- The classification of variants should always be based on all available, preferentially quantitative, information including data from functional analyses, segregation analyses, large case-control studies and population databases such as gnomAD should be taken into account.

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Multimodal Intensified Surveillance Program (IFNP)

	Oxford		
	LoE	GR	AGO
The IFNP with the addition of MRI, breast ultrasound and mammogram			++
<ul style="list-style-type: none"> should be used for <i>BRCA1/2</i> pV carriers can be used for pV carriers of other risk genes for breast cancer can be used for tested women without evidence of pV between 30 and 50 years with a breast cancer risk of $\geq 5\%$ in 10 years can be used in follow-up care after initial disease ≤ 45 years, fulfillment of the FBREK criteria and without evidence of pV 			
as part of systematically collected, transparent quality assurance and corresponding evaluation of results.			
<ul style="list-style-type: none"> For detection of early stage breast cancers 	2a	B	++
<ul style="list-style-type: none"> For improvement of metastasis-free interval 	2b	B	+
<ul style="list-style-type: none"> For mortality reduction (10-year survival) 	3a	C	+/-
Patients who have undergone therapeutic radiation of the chest wall in childhood and adolescence (e.g. Hodgkin's disease, see S3 guideline Hodgkin's disease) can be included in the-Surveillance Program			

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2. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Mammakarzinoms, Version 4.4, 2021, AWMF Registernummer: 032-045OL, <http://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom/> (abgerufen am: 24.1.2022) 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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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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High-Risk Breast Cancer Surveillance with MRI


	30-39 years		40-49 years		≥ 50 years	
	Detection rate (‰)	PPV (%)	Detection rate (‰)	PPV (%)	Detection rate (‰)	PPV (%)
<i>BRCA1</i>	43.2	29.4	21.8	25.5	30.5	33.3
<i>BRCA2</i>	22.7	23.3	24.3	27.5	16.3	23.5
<i>BRCA1/2</i> -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 (healthy women).

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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Modified Surveillance Program for BRCA-neg. Women at Moderate to High Risk or Survivors of Hodgkin Disease

Rationale:

- Increased risk of breast cancer after chest irradiation because of Hodgkin lymphoma in childhood (9-18 years)
- Increased risk of breast or ovarian cancer in women from *BRCA1/2* negative families at risk that is, however, lower than in women from *BRCA1/2* positive families
- Referral to centres of the GC-HBOC or cooperating centres for the evaluation of structured surveillance and follow-up

1. E-Learning DKG/FBREK, 2022
2. Eisenberg ER, Weiss A, Prakash I et al. Surgical Management and Contralateral Breast Cancer Risk in Women with History of Radiation Therapy for Hodgkin Lymphoma: Results from a Population-Based Cohort. *Ann Surg Oncol*. 2022 Oct;29(11):6673-6680.
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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	++
<p>The lifetime risk of breast cancer in the general male population is 0.1% the lifetime risk for prostate cancer is 10-12%. <i>BRCA1</i> mutation carriers have a risk of breast cancer until 80 years of age of about 0,4% and a risk for prostatic cancer as in the general male population.</p> <p><i>BRCA 2</i> mutation carriers have an up to 4% lifetime risk for breast cancer and a lifetime risk up to 30% for prostatic cancer.</p>			
* 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	--

RRME ohne gentisches Risiko:

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](http://dx.doi.org/10.1016/S1470-2045(17)30891-4).

Sentinel-Lymphknoten Exzision bei RRME:

1. Wong SM, Ferroum A, Apostolova C et al. Incidence of Occult Breast Cancer in Carriers of BRCA1/2 or Other High-Penetrance Pathogenic Variants Undergoing Prophylactic Mastectomy: When is Sentinel Lymph Node Biopsy Indicated? Ann Surg Oncol. 2022 Oct;29(11):6660-6668.

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

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)** <ul style="list-style-type: none"> Reduces OvCa incidence and mortality Reduces overall mortality 	2a	B	
<ul style="list-style-type: none"> Risk-reducing bilateral mastectomy (RR-BM) <ul style="list-style-type: none"> Reduces BC incidence Reduces BC mortality in <i>BRCA1</i> 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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- 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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- 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.
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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.

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

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ▪ Risk-reducing bilateral salpingo-oophorectomy (RR-BSO) <ul style="list-style-type: none"> ▪ Reduces OvCa incidence and mortality ▪ Reduces overall mortality (contradictory results for reduction of cl BC incidence) 	2b	B	+*
<ul style="list-style-type: none"> ▪ Prophylactic contralateral mastectomy (RR-CM)* <ul style="list-style-type: none"> ▪ Reduces BC incidence and mortality 	2b	B	+*
<ul style="list-style-type: none"> ▪ Tamoxifen (reduces contralateral BC incidence) 	2b	B	+/-*
<ul style="list-style-type: none"> ▪ Indication for RR-CM should consider age at onset of first breast cancer in affected gene 	2a	B	++*
<ul style="list-style-type: none"> ▪ 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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Medical Prevention for Women at Increased Risk

- **Tamoxifen for women > 35 years:**
Risk reduction of invasive BC, DCIS and LN
- **Raloxifen for postmenopausal women:**
Risk reduction of invasive BC only
- **AI for postmenopausal women**

Oxford		
LoE	GR	AGO
1a	A	+*
1b	A	+*
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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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.
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