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Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Breast Cancer Risk and Prevention



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Breast Cancer Risk and Prevention

- **Versions 2003–2019:**
Schmutzler mit Albert / Bischoff / Blohmer / Ditsch / Fasching / Fehm / Kiechle / Maass / Müller-Schimpfle / Mundhenke / Rhiem / Rody / Schmidt / Schmutzler / Stickeler / Thomssen /
- **Version 2020:**
Fasching / Rhiem

Principles of Prevention

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

(Primum nil nocere)



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Who Should be Tested for *BRCA1/2* Mutations and Possibly Further Risk Genes? (Part 1 of 2)

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

Families with (each from one family branch)*


- at least three women with breast cancer independent of age or
- at least two women with breast cancer, one < 50 yrs. or
- at least one woman affected by breast and one by ovarian cancer or
- at least one woman affected by breast and ovarian cancer or
- at least two women affected by ovarian cancer or
- at least one woman affected by bilateral breast cancer, first < 50 yrs. or

* Inclusion criteria of the German Consortium of Hereditary Breast and Ovarian Cancer (GCHBOC) based on a *BRCA1/2* mutation prevalence ≥ 10% tested in 21,401 families. All mutation carriers should be registered in scientific databases, to validate the inclusion and exclusion criteria (including population-based studies).

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. Fasching PA, Loibl S, Eidtmann H, et al. BRCA mutations, therapy response and prognosis in the neoadjuvant GeparQuinto study. *Cancer Res.* 2016;76:(4 Suppl):Abstract nr S5-06.
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cancer patients (AGO-TR1). PLoS One 2017;12:e0186043. - neu

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9. 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. – neu
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11. Couch FJ, Hu C, Hart SN et al.: Age-related breast cancer risk estimates for the general population based on sequencing of cancer predisposition genes in 19,228 breast cancer patients and 20,211 matched unaffected controls from US based cohorts in the CARRIERS study GS2-01, oral presentation, SABCS 2018
12. Manchanda R, Gaba F. Population Based Testing for Primary Prevention: A Systematic Review. *Cancers (Basel)*. 2018 Nov 5;10(11).



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Who Should be Tested for *BRCA1/2* Mutations and Possibly Further Risk Genes? (Part 2 of 2)

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

Families with (each from one family branch)*

- at least one woman affected by breast cancer < 35 yrs. or
- at least one man affected by breast cancer and one additional relative affected by breast or ovarian cancer
- Other recommended criteria:
 - own disease of triple negative breast cancer ≤ 60 yrs. of age
 - own disease of ovarian cancer
 - if therapeutically relevant (e.g. PARPi)

* Inclusion criteria of the German Consortium of Hereditary Breast and Ovarian Cancer (GCHBOC) based on a *BRCA1/2* mutation prevalence ≥ 10% tested in 21,401 families. All mutation carriers should be registered in scientific databases, to validate the inclusion and exclusion criteria (including population-based studies).

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.
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cancer patients (AGO-TR1). PLoS One 2017;12:e0186043.

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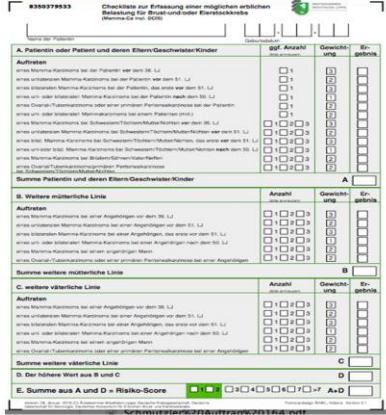
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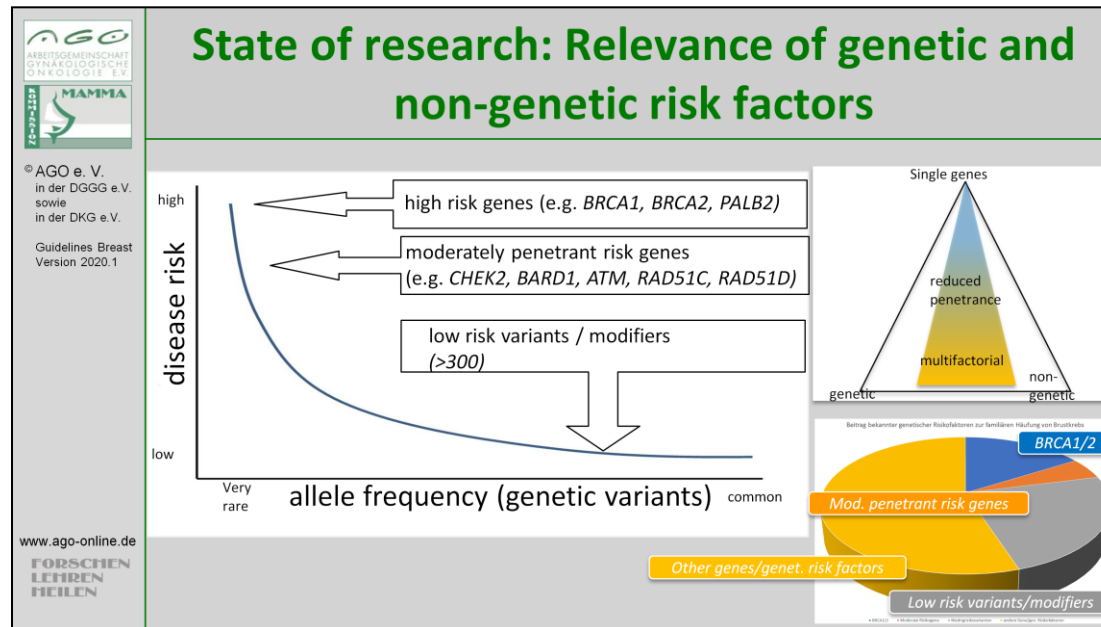
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Checklist according to Public Health Insurance Policies (German GKV#)*



* online tool provided by the Ärztekammer Westfalen-Lippe in cooperation with the GC-HBOC based on the inclusion criteria of the GC-HBOC (Kast et al., J Med Genet 2016;53:465-71)
<https://www.aekwl.de/fileadmin/qualitaetssicherung/Zertifizierungsstelle/2018-07-17-CL-Genetik.pdf>

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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.
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Breast Cancer Risk Genes with moderate to high Lifetime Risk

For following genes, risk calculations are available with varying degree of evidence. The clinical benefit must be proven by the effectiveness of preventive measures. ORs from studies with selected populations cannot be transferred to other populations.

	Oxford		
Clinical benefit of genetic test	LoE	GR	AGO
■ <i>BRCA1</i> (#), <i>BRCA2</i> *	1b	A	++ [°]
■ <i>PALB2</i> (#), <i>CDH1</i> , <i>TP53</i> **	3a	B	+/- [°]
■ <i>ATM</i> , <i>CHEK2</i> , <i>BARD1</i> (#), <i>RAD51C</i> , <i>RAD51D</i> ***	3a	B	+/- [°]

* *BRCA1/2* are genes with a high lifetime risk. Furthermore genes with a medium and a low lifetime risk have been described.

** High ORs allow for the assumption that these are high risk genes. Prospective and age-related penetrances are not yet available.

***These genes are classified as genes with a moderate lifetime risk based on currently available data.


(#) These genes are associated with an increased risk of triple-negative breast cancer.

[°] Participation in prospective registries or studies is highly recommended.

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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Current Clinical Impact of Further Risk Genes

- Further moderate and low-risk gene variants are most likely transmitted by an oligo- or polygenic trait.
- The penetrance of such genes depends on the own and family cancer history.
- Single low-risk variants confer only small risk elevations and also seem to be associated with specific tumor subtypes. Potential multiplicative effects that may be relevant for risk stratification and provision of clinical prevention strategies remain to be elucidated. Therefore, the analysis of multiple gene regions may be of clinical relevance in the future.
- Therefore, genetic testing of moderate and low-risk genes and variants should only be performed within large prospective cohort studies like the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC).

	Oxford		
	LoE	GR	AGO
▪ Clinical genetic testing of moderate-risk genes, e.g. gene panels	3a	B	+/-
▪ Clinical genetic testing for low-risk variants	3b	D	--
▪ Referral to centers of the GC-HBOC or cooperating centers	5	D	+

1. 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.
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Non BRCA-associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer

Syndrome	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-Syndrome)	<i>ATM</i>	breast cancer, leukemia, stomach, melanoma, sarcoma
Franconi Anämie	<i>BRCA2, BRIP1, RAD51C, PALB2</i>	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.
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Current version of the TruRisk® BC/OC* Gene Panel by the German Consortium (GC-HBOC)

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



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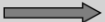
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Distinct Genetically Subtypes Defines Distinct Tumor Entities

Distinct genetic subtypes of breast cancer may show distinct clinical features. Prior to the offer risk reducing clinical procedures the following facts and data should be addressed:

- Age related disease penetrance?
- Typical histopathological features?
- Sensitivity to current screening modalities?
- Better survival of early detected tumors?
- Natural disease course?
- Response to anti-tumor therapy?


Genotype-phenotype-correlations must be known before performing preventive clinical measures

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VUS: Problems and Questions

- „A Variant of Unknown Significance (VUS IARC class 3) is a genetic variant with unknown clinical relevance.“ (Plon et al. Hum Mutat 2008)
- Most VUS are extremely rare (≤ 3 variants in $>80\%$ of families)
- Classification of sequence variants should be performed according to the IARC classification system
- Frequency of VUS (IARC class 3) increases with numbers of tested genes
- Clinical interpretation and decision making depending on the IARC classification system is not standardized yet
- In silico prediction tools (PolyPhen2, SIFT) are not adequate or sufficient for clinical decision making
- Additional analyses are required, e.g. in vitro splicing assay, functional assay, segregation analysis, co-occurrence analysis, large case / control studies

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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

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			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 no of 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.



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Classification of IARC Class 3 Variants

Requires additional information and analyses, e.g.

- **Co-occurrence data from large data banks**
- **Segregation analysis**
- **Functional analysis etc.**
- **Data should be pooled in large study groups (e.g. ENIGMA)**

*Most class 3 variants can be downgraded to clinically irrelevant classes 1 or 2 by these analyses. Few are upgraded to the clinically relevant classes 4 or 5. Any re-evaluation of the IARC class should be communicated to the tested persons (see for example the concept of supervision in centres of the German Consortium/GC-HBOC).

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Requirements for the Introduction of New Diagnostic or Predictive Genetic Testing*

- The risk collective is clearly defined by risk criteria.
- The positive predictive value of risk criteria with respect to the identification of the genetic risk factor is known.
- The cut-off values for genetic testing evolved through a transparent consensus process.
- The genetic test is valid and reliable.
- A spectrum bias is excluded or defined.
- A clinical prevention strategy exists that leads to early detection or prevention and mortality reduction of the genetically defined subset of the disease.

* Acc. to the position paper on risk-adjusted early detection of cancer of the German National Cancer Plan developed under the Federal Ministry of Health, e.g. "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. Schmutzler RK, et al. Risikoadaptierte Früherkennung, Ein Papier der Unterarbeitsgruppe „Risikoadaptierte Früherkennung der AG1 „Weiterentwicklung der Krebsfrüherkennung“ des Nationalen Krebsplans.
http://www.bmgbund.de/fileadmin/dateien/Downloads/N/Nationaler_Krebsplan/Zielepapier_zum_Querschnittsthema_Risiko-adaptierte_Krebsfrueherkennung.pdf. 2011.
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Non-Directive Counseling regarding Preventive Measures

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LoE	GR	AGO
5	D	++

- According to the Genetic Diagnostic Law
- According to the Medical Devices Act,
e.g. risk assessment requires professional training and expertise
- Application of software for risk calculation requires professional training and experience
- Communicate absolute risks within a manageable timeframe
- Communicate risk and benefit of a multimodal intensive surveillance program
- Communicate risk and benefit of preventive clinical methods
- Communicate competing risks, e.g. risk of disease progression in relation to risk of a secondary primary in case women already affected by primary breast cancer
- Allow appropriate time for consideration

1. Phi XA, Houssami N, Hooning MJ et al., Accuracy of screening women at familial risk of breast cancer without a known gene mutation.. Eur J of Cancer 2017;85:31-38
2. Aktualisierte Empfehlungen nach Bewertung von Gdablagerungen im Gehirn und anderen Geweben (08.01.2018) durch EMA und BfArM



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Multimodal Intensive Surveillance Program*

		Oxford		
		LoE	GR	AGO
<ul style="list-style-type: none"> ■ Program für BRCA-Carriers ■ For the detection of early stage cancers <ul style="list-style-type: none"> ■ Clinical breast exam > = 25 Jahre ■ Sonographie > = 25 Jahre ■ Mammogram > = 40 Jahre ■ Breast MRI > = 25 Jahre ■ For improvement of metastasis-free interval ■ Survivors after tumors in childhood and radiotherapy of thoracic wall (e.g. M. Hodgkin) 		<div style="border-bottom: 1px solid green; margin-bottom: 5px;">2b</div> <div style="border-bottom: 1px solid green; margin-bottom: 5px;">Semi-annually</div> <div style="border-bottom: 1px solid green; margin-bottom: 5px;">Semi-annually</div> <div style="border-bottom: 1px solid green; margin-bottom: 5px;">Bi-annually</div> <div style="border-bottom: 1px solid green; margin-bottom: 5px;">Annually</div> <div style="border-bottom: 1px solid green; margin-bottom: 5px;">2b</div> <div style="border-bottom: 1px solid green; margin-bottom: 5px;">2a</div>	<div style="border-bottom: 1px solid green; margin-bottom: 5px;">B</div> <div style="border-bottom: 1px solid green; margin-bottom: 5px;">B</div> <div style="border-bottom: 1px solid green; margin-bottom: 5px;">B</div> <div style="border-bottom: 1px solid green; margin-bottom: 5px;">B</div> <div style="border-bottom: 1px solid green; margin-bottom: 5px;">B</div> <div style="border-bottom: 1px solid green; margin-bottom: 5px;">B</div>	<div style="border-bottom: 1px solid green; margin-bottom: 5px;">++</div> <div style="border-bottom: 1px solid green; margin-bottom: 5px;">+</div> <div style="border-bottom: 1px solid green; margin-bottom: 5px;">++</div>

* The multimodal intensified early detection program should be carried out within the framework of transparent quality assurance and appropriate evaluation.

1. 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.
2. Kriege M, Brekelmans CT, Boetes C, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med. 2004;351(5):427-37.
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6. 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
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8. Ellen Warner: Screening BRCA1 and BRCA2 Mutation Carriers for Breast Cancer. Review. *Cancers* 2018, 10, 477; doi:10.3390/cancers10120477
9. 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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High risk screening including MRI

- A cohort of 4,573 high-risk, previously unaffected women (954 BRCA1 carriers, 598 BRCA2 carriers, 3,021 BRCA1/2 non-carriers) participated.
- Screening outcomes for 14,142 screening rounds with MRI between 2006 and 2015 were analyzed and stratified by risk group, type of screening round, and age.
- A total of 221 primary breast cancers (185 invasive, 36 in situ) was detected.
- 84.5% (174/206, 15 unknown) were stage 0 or I.
- Program sensitivity was 89.6% (95%CI 84.9-93.0) with no significant differences in sensitivity between risk groups or by age.
- Of all cancers, only 1,4 % were symptomatic interval cancers.
- The rate of MRI-only- detected cancers was 15/71 in BRCA 1 carriers (21%), 17/47 in BRCA 2 carriers (36%), and 29/80 high risk BRCA 1,2 non carriers (36%).
- The rate of MG-only detected cancers was 7/198 cases, the rate of US-only cancers 2/198 cases (BRCA 1 carriers in the 6 month interval of first round).

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

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, doi: 10.1007/s10549-019-05152-9

High risk screening including MRI


Table 5 Detection performance of annual multimodality screening rounds with MRI by risk group, type of screening round and age

	No. of rounds	No. of cancers	Detection rate		Sensitivity		Specificity		PPV	
			%	95% CI	%	95% CI	%	95% CI	%	95% CI
<i>BRCA1</i> carriers	2,750	83	25.5	20.2 to 32.0	84.3	75.0 to 90.6	90.1	88.9 to 91.2	21.0	17.0 to 25.7
First rounds	954	24	19.9	12.8 to 30.9	79.2	59.5 to 90.8	86.2	83.9 to 88.3	12.9	8.4 to 19.3
Subsequent rounds	1,796	59	28.4	21.7 to 37.1	86.4	75.5 to 93.0	92.2	90.9 to 93.4	27.4	21.5 to 34.2
<30 years	247	3	8.1	2.2 to 29.0	66.7	20.8 to 93.9	94.3	90.6 to 96.6	12.5	3.5 to 36.0
30–39 years	579	28	43.2	29.4 to 63.0	89.3	72.8 to 96.3	89.1	86.2 to 91.4	29.4	20.8 to 39.8
40–49 years	642	17	21.8	13.0 to 36.3	82.4	59.0 to 93.8	93.4	91.2 to 95.1	25.5	15.8 to 38.3
≥50 years	328	11	30.5	16.6 to 55.2	90.9	62.3 to 98.4	93.7	90.5 to 95.9	33.3	19.2 to 51.2
<i>BRCA2</i> carriers	1,724	53	27.8	21.1 to 36.7	90.6	79.7 to 95.9	90.2	88.7 to 91.6	22.7	17.6 to 28.9
First rounds	598	27	43.5	29.8 to 62.9	96.3	81.7 to 99.3	85.1	82.0 to 87.8	23.4	16.5 to 32.1
Subsequent rounds	1,126	26	19.5	12.9 to 29.4	84.6	66.5 to 93.8	92.9	91.2 to 94.3	22.0	15.0 to 31.1
<30 years	119	0	0.0	0.0 to 31.3			89.1	82.2 to 93.5	0	0.0 to 22.8
30–39 years	309	9	22.7	11.0 to 46.0	77.8	45.3 to 93.7	92.3	88.8 to 94.8	23.3	11.8 to 40.9
40–49 years	452	12	24.3	13.6 to 43.0	91.7	64.6 to 98.5	93.4	90.7 to 95.4	27.5	16.1 to 42.8
≥50 years	246	5	16.3	6.3 to 41.1	80.0	37.6 to 96.4	94.6	91.0 to 96.8	23.5	9.6 to 47.3
<i>BRCA1/2</i> non-carriers with high risk	9,668	85	8.3	6.7 to 10.3	94.1	87.0 to 97.5	88.5	87.9 to 89.2	6.8	5.5 to 8.4
First rounds	3,021	41	13.6	10.0 to 18.4	100	91.4 to 100	84.1	82.7 to 85.3	7.9	5.9 to 10.6
Subsequent rounds	6,647	44	5.9	4.3 to 8.0	88.6	76.0 to 95.0	90.6	89.8 to 91.2	5.9	4.3 to 8.0
<30 years	481	0	0.0	0.0 to 7.9			93.6	91.0 to 95.4	0	0.0 to 11.0
30–39 years	2,089	6	2.9	1.3 to 6.3	100	61.0 to 100	90.2	88.8 to 91.4	2.8	1.3 to 6.1
40–49 years	3,254	28	7.4	5.0 to 11.0	85.7	68.5 to 94.3	89.7	88.6 to 90.7	6.8	4.6 to 9.9
≥50 years	823	10	10.9	5.8 to 20.7	90.0	59.6 to 98.2	93.1	91.2 to 94.7	13.8	7.5 to 24.3
Total	14,142	221	14.0	12.2 to 16.1	89.6	84.9 to 93.0	89.1	88.5 to 89.6	11.5	10.1 to 13.1

CI confidence interval, PPV positive predictive value

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

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, doi: 10.1007/s10549-019-05152-9



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Surveillance Program for Female Carriers of Pathogenic BRCA Mutations after Primary Breast Cancer acc. to GC-HBOC *

		Oxford		
		LoE	GR	AGO
<ul style="list-style-type: none"> ■ Multimodal intensive lifelong surveillance program ■ For detection of early stage breast cancers <ul style="list-style-type: none"> ■ Clinical breast exam > = 25 Jahre Semi-annually ■ Sonographie > = 25 Jahre Semi-annually ■ Mammogram > = 40 Jahre Biannually ■ Breast MRI (until ACR1) > = 25 Jahre Annually ■ For mortality reduction (10-year survival) 				
		2a	B	++
		3a	C	+/-*

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

1. 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.
2. Kriege M, Brekelmans CT, Boetes C, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med. 2004;351(5):427-37.
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8. 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



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Breast Cancer Risk Genes with moderate to high Lifetime Risk

BRCA1 mutation carriers have a risk of breast cancer corresponding to the general population (about 1%) and an up to 1.8 to 3.75 times higher risk for prostatic cancer $\leq 65y$.

BRCA 2 mutation carriers have an up to 5–7% lifetime risk for breast cancer and an up to 2.5 to 8.6 times higher risk for prostatic cancer $\leq 65y$.


	Oxford LoE	GR	AGO
Currently, no specific surveillance is recommended			
▪ For breast cancer: self examination and watchful waiting	5	D	+
▪ For prostate cancer: Compare recommendations on prostate carcinoma (https://www.prostatakrebs-bps.de/images/DGU-Stellungnahme_PSA_Pressemappe_2019.pdf)	3b	C	+

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

1. 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.
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12. 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



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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. 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.
2. Kriege M, Brekelmans CT, Boetes C, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. *N Engl J Med*. 2004;351(5):427-37.
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[Dtsch Arztebl Int.](#) 2014 Jan 6;111(1-2):3-9. doi: 10.3238/arztebl.2014.0003.

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.

[Schellong G¹](#), [Riepenhausen M](#), [German Consortium for Hereditary Breast and Ovarian Cancer](#) et al.



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Surgical Prevention

Oxford		
LoE	GR	AGO
2a	B	+*


- **A secondary risk-reducing unilateral or bilateral mastectomy is not indicated without the presence of clearly defined genetic risk factors because it does not lead to a reduction in mortality.**

* study participation recommended

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).



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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*** 	2a	B	+*
	2b	B	+*

* study participation recommended

** The RRSO is recommended from about 35 years for *BRCA1* and from about 40 years for *BRCA2* mutation carriers, taking into account the age of ovarian cancer diagnosis in the family and the family planning status.

*** No reduction in mortality could be shown for *BRCA2* mutation carriers. RRM counselling should be individualised.


1. Sitzmann JV, Wiebke EA. Risk-reducing appendectomy and the elimination of *BRCA1*-associated intraperitoneal cancer. *JAMA Surg.* 2013;148(3):285-91; discussion 91.
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Risk-reducing Interventions for BRCA1/2 Female Mutation Carriers <u>Affected</u> 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-M should consider age at onset of first breast cancer in affected gene 	2a	B	++*
<ul style="list-style-type: none"> ■ RR-M after ovarian cancer 	4	C	+/-**
* study participation recommended ** Depends on tumor stage (FIGO I/II), recurrence free interval (≥ 5y), age			

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Improved Overall Survival After Contralateral Risk-reducing Mastectomy in BRCA1/2 Mutation Carriers


Improved overall survival after contralateral risk-reducing mastectomy in BRCA1/2 mutation carriers with a history of unilateral breast cancer: a prospective analysis.

Heemskerk-Gerritsen BA1, Rookus MA, Aalfs CM, Ausems MG, Collée JM, Jansen L, Kets CM, Keymeulen KB, Koppert LB, Meijers-Heijboer HE, Mooij TM, Tollenaar RA, Vasen HF; HEBON, Hoening MJ, Seynaeve C.

Int J Cancer. 2015 Feb 1;136(3):668-77. doi: 10.1002/ijc.29032. Epub 2014 Jul 8.

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


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Therapy of <i>BRCA1/2</i> -associated Breast Cancer			
 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	Limited prospective cohort studies with short follow-up time		
	■ Breast conserving surgery: adequate local tumor control (~10 years observation)	2a	B +
	■ Systemic therapy according to sporadic breast cancer	3a	B +
	■ gBRCA mutation status is predictive for chemotherapy response in TNBC	2b	B +
	■ Carboplatin (vs. Docetaxel) in metastatic breast cancer	2b	B +
	■ PARP inhibitor in metastatic breast cancer	1b	B +

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Medical Prevention for Women at Increased Risk

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


[#] 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.

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

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Risk Reduction for Ipsi- and Contralateral Breast Cancer

Rationale: Women with breast cancer have an increased risk for a second primary

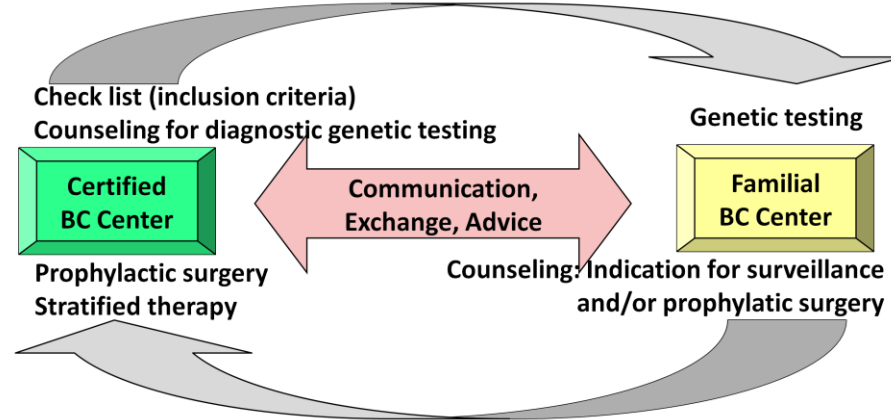
- Tamoxifen*
- Aromatase inhibitors*
- Suppression of ovarian function* + Tamoxifen

Oxford		
LoE	GR	AGO
1a	A	+
1a	A	+
1b	B	+

* Only proven for ER/PgR-positive primary sporadic BC

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



* trans-sectoral contract for integrated care, acc. to code of social law § 140a since 2015