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Guidelines Breast
Version 2022.1E

Breast Cancer Risk, Genetics and Prevention

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Breast Cancer Risk and Prevention

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

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

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)

Indication for Genetic Testing of *BRCA1/2* Genes and Possibly Further Risk Genes?

(Part 1 of 2 – testing according to family history)

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

Families with (each from one family branch) at least*

- **three women with breast cancer independent of age or**
- **two women with breast cancer, one < 50 yrs. (before the 51st birthday) or**
- **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 the 51st birthday**
- **one woman affected by breast cancer < 35 yrs. (before the 36th birthday) or**
- **one man affected by breast cancer and one additional relative affected by breast or ovarian cancer**

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* **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).

Indication for Genetic Testing of *BRCA1/2* Genes and Possibly Further Risk Genes?

(Part 2 of 2 - testing according to disease)

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

- **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)**

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Checklist for Recording a Possible Hereditary Burden of Breast and / or Ovarian Cancer

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Name Patientin/Patient: 　　　　　Geburtsdatum:

DKG KREBSGESELLSCHAFT Zertifizierung

Ausfüllhinweis

A. Patient/in und deren Geschwister / Kinder

Auftreten bei Patientin/Patient	Anzahl	Gewichtung	Ergebnis
eines Mammakarzinoms bei der Patientin **vor** dem 36. Geburtstag		3	0
eines triple-negativen Mammakarzinoms bei der Patientin vor dem 60. Geburtstag*		3	0
eines unilateralen Mammakarzinoms bei der Patientin **vor** dem 50./51.* Geburtstag		2	0
eines bilateralen Mammakarzinoms bei der Patientin, das erste **vor** dem 50./51.* Geburtstag		3	0
eines uni- oder bilateralen Mammakarzinoms bei der Patientin **nach** dem 51. Geburtstag		1	0
eines uni- oder bilateralen Mammakarzinoms bei den Patienten (männlich)		2	0
eines Ovarialkarzinoms bei der Patientin vor dem 80. Geburtstag*		3	0
eines Ovarial-/Tuben-/primären Peritonealkarzinoms bei der Patientin		2	0

Auftreten bei Kindern, Geschwistern und deren Kindern	Anzahl	Gewichtung	Ergebnis
eines Mammakarzinoms bei Schwestern/Töchtern/Nichten **vor** dem 36. Geburtstag		3	0
eines unilateralen Mammakarzinoms bei Schwestern/Töchtern/Nichten **vor** dem 50./51.* Geburtstag		2	0
eines bilateralen Mammakarzinoms bei Schwestern/Töchtern/Nichten, das erste **vor** dem 50./51.* Geburtstag		3	0
eines uni- oder bilateralen Mammakarzinoms bei Schwestern/Töchtern/Nichten **nach** dem 51. Geburtstag		1	0
eines uni- oder bilateralen Mammakarzinoms bei Brüdern/Söhnen/Neffen		2	0
eines Ovarial-/Tuben-/primären Peritonealkarzinoms bei Schwestern/Töchtern/Nichten		2	0
		A	0

B. Mütterliche Linie (incl. Mutter)

Auftreten	Anzahl	Gewichtung	Ergebnis
eines Mammakarzinoms bei einer Angehörigen **vor** dem 36. Geburtstag		3	0
eines unilateralen Mammakarzinoms bei einer Angehörigen **vor** dem 50./51.* Geburtstag		2	0
eines bilateralen Mammakarzinoms bei einer Angehörigen, das erste **vor** dem 50./51.* Geburtstag		3	0
eines uni- oder bilateralen Mammakarzinoms bei einer Angehörigen **nach** dem 51. Geburtstag		1	0
eines Mammakarzinoms bei einem angehörigen Mann		2	0
eines Ovarial-/Tuben-/primären Peritonealkarzinoms bei einer Angehörigen		2	0
Summe weitere mütterliche Linie			
		B	0

C. Väterliche Linie (incl. Vater)

Auftreten	Anzahl	Gewichtung	Ergebnis
eines Mammakarzinoms bei einer Angehörigen **vor** dem 36. Geburtstag		3	0
eines unilateralen Mammakarzinoms bei einer Angehörigen **vor** dem 50./51.* Geburtstag		2	0
eines bilateralen Mammakarzinoms bei einer Angehörigen, das erste **vor** dem 50./51.* Geburtstag		3	0
eines uni- oder bilateralen Mammakarzinoms bei einer Angehörigen **nach** dem 51. Geburtstag		1	0
eines Mammakarzinoms bei einem angehörigen Mann		2	0
eines Ovarial-/Tuben-/primären Peritonealkarzinoms bei einer Angehörigen		2	0
Summe väterliche Linie			
		C	0

D. Der höhere Wert aus B und C → D 0

E. Summe aus A und D = Risiko-Score → A+D 0

Zunächst wird die Anzahl bekannter Erkrankungsfälle bei den Geschwistern und Kindern, einschließlich der aktuellen Erkrankung der Patientin sowie in der mütterlichen und väterlichen Linie erfragt.

Diese Zahlen werden mit den jeweiligen Gewichtungen multipliziert. Dann wird die Summe aus diesen Ergebnissen errechnet und in die Felder A und B und C eingetragen.

Der höhere der beiden Werte aus den Feldern B und C wird in Feld D eingetragen.

Der Gesamtscore errechnet sich dann aus der Summe der Felder A und D.
Eine Risikoberatung in den ausgewiesenen Zentren ist bei Scores ≥ 3 Punkten zu empfehlen
*Diese Einschlusskriterien gelten nur in Kooperation mit den Zentren des Deutschen Konsortiums Familiärer Brust- und Eierstockkrebs bzw. mit den zertifizierten FBREK-Zentren , die diese im Rahmen der Wissen generierenden Versorgung validieren. Die anderen Einschlusskriterien entsprechen den Vorgabe des EBM.
Version: 11. Januar 2022 (C)
Ärztekammer Westfalen-Lippe,
Deutsche Krebsgesellschaft,
Deutsche Gesellschaft für Senologie,
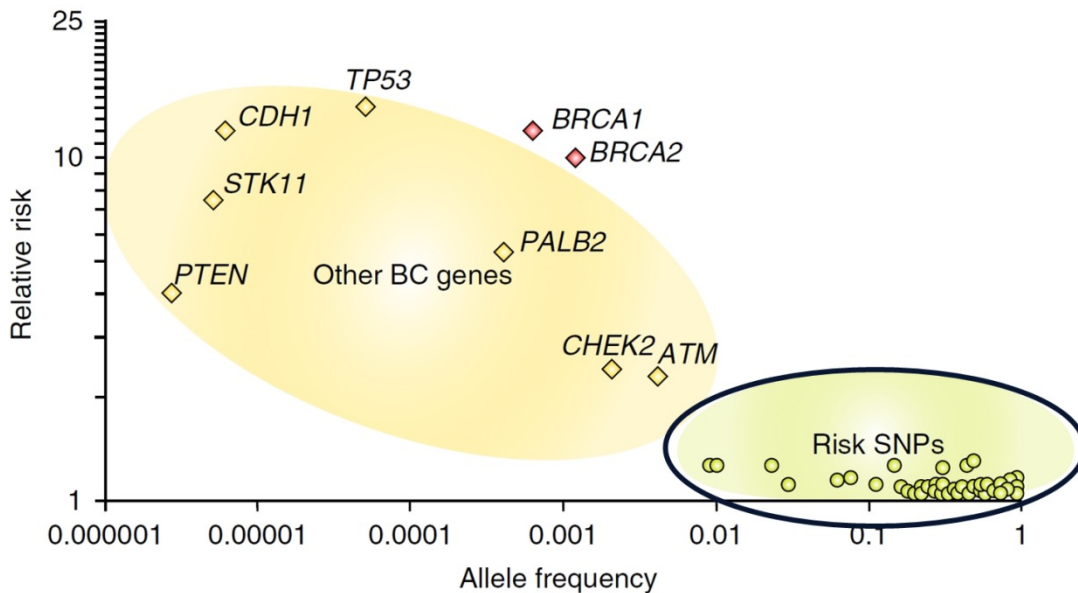Deutsches Konsortium für Erblichen Brust- und Eierstockkrebs

https:///
checkliste_erbliche_belastung_brust_gyn-210212

online tool provided by the GC-HBOC,
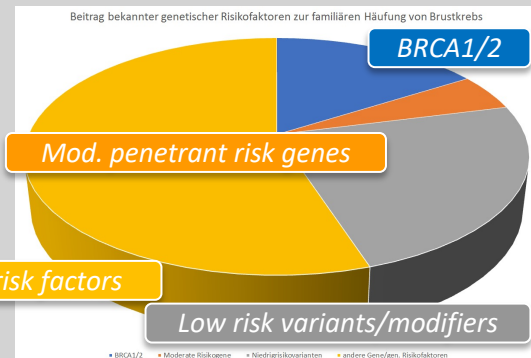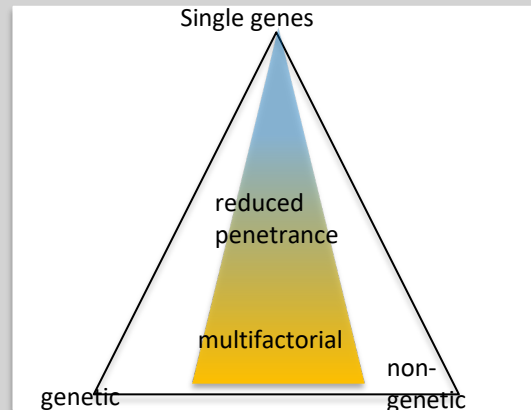**https://familiaerer-brust-und-eierstockkrebs.uk-koeln.de/informationen/downloads/**

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

Turnbull et al. (2018). "Cancer genetics, precision prevention and a call to action." Nature Genetics **50**(9): 1212-1218.

Beitrag bekannter genetischer Risikofaktoren zur familiären Häufung von Brustkrebs

BRCA1/2

Mod. penetrant risk genes

Other genes/genet. risk factors

Low risk variants/modifiers

Pathogenic Variants with Moderate to High Lifetime Risk for Breast Cancer

	Oxford		
	LoE	**GR**	**AGO**
Age-related risks for breast cancer			
▪ high: *BRCA1, BRCA2, PALB2*			
▪ high: *CDH1, PTEN, TP53; STK11#*			
▪ moderate: *ATM, CHEK2*			
▪ moderate: B*ARD1, RAD51C, RAD51D*			
Clinical benefit* of a genetic test			
▪ *BRCA1, BRCA2*	1b	A	++°
▪ *PALB2*	3a	B	+°
▪ *CDH1, PTEN, TP53, STK11*	3b	B	+°
▪ *ATM, BARD1, CHEK2, RAD51C, RAD51D*	3a	B	+/- °

* Take into account the effectiveness of preventive measures and competing risks when making clinical decisions.

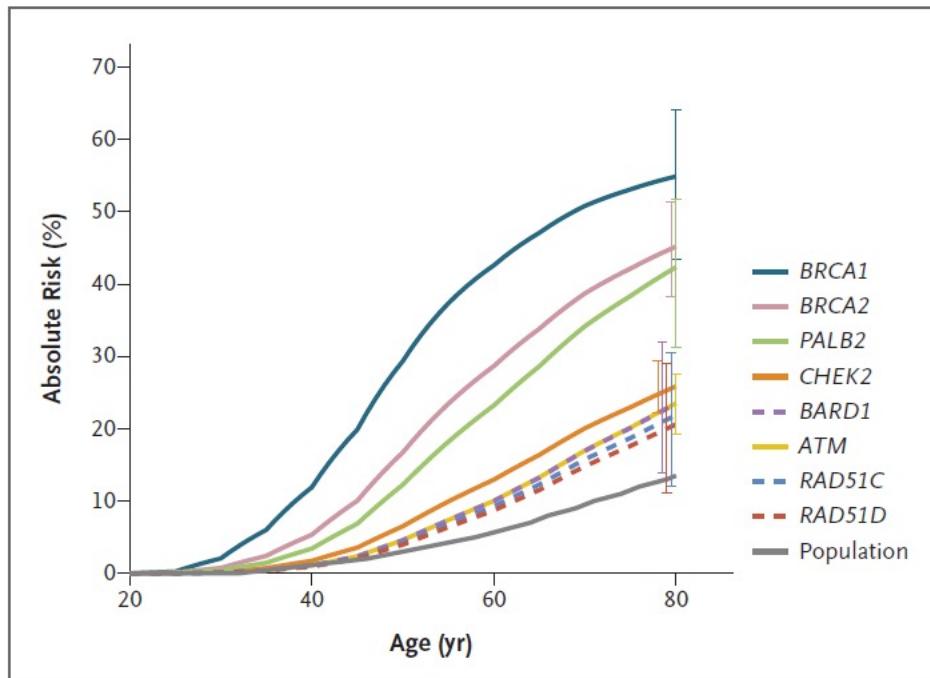° Participation in prospective registries or studies is highly recommended.

Breast Cancer Risk Category

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

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.

Management of Individuals with Germline Variants in PALB2: A Clinical Practice Resource of the American College of Medical Genetics and Genomics (ACMG)

Conclusion:

The recommendations made here have been based on expert opinion using comprehensive literature ascertainment approach, but not systematic review. There is strong evidence that P/LP *PALB2* variants confer a range of breast cancer risks across what is considered moderate to high; consequently, enhanced surveillance and the option of risk-reducing interventions are warranted.

The risk range for this gene underlies the need to move away from compartmentalizing PALB2 and consider risk to be a continuous variable from high to moderate, influenced by family history, polygenic risk score, and other factors. The same applies to other breast cancer genes.

Changing this paradigm will allow us **to move to personalized risk estimates by placing the risk from the P/LP variant in the context of other risk factors and develop strategies to translate this information to enhance medical management.**
There is reasonable evidence that **PALB2** P/LP variants confer a small to moderately increased risk for ovarian cancer that may warrant risk-reducing interventions, albeit their clinical benefit is not sufficiently proven yet with respect to the efficacy of preventive measures to reduce morbidity and mortality. …

Given the many uncertainties, those at risk for *PALB2*-related cancers, and the health professionals who care for them are encouraged to contribute follow-up data to long term studies, thereby facilitating the generation of prospective cancer risk estimates and the evaluation of prevention measures…

Tischkowitz M, Balmaña J, Foulkes WD, et al. Management of individuals with germline variants in PALB2: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23(8):1416-1423. doi:10.1038/s41436-021-01151-8

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.**
- **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 in the future.**

	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)	2b	B	+/-*
Referral to centers of the GC-HBOC or cooperating 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.

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

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

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	SMARCA4	STK11	APC	FAM175A	FANCC	FANCM	HOXB13
MEN1	MRE11A	MUTYH	NBN	NF1	POLD1	POLE	RAD50
RECQL	XRCC2						

Selection of genes:	**11 BC (breast cancer) / OC (ovarian cancer) 'core genes'** (Data on risk increase)
	7 other s**yndrome-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	

TruRisk® V3.1.1.   *** BC = breast cancer, OC = ovarian cancer**

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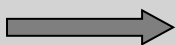
Genotype-phenotype-correlations must be known before performing preventive clinical measures

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 <u>extremely rare</u> (≤ 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-occurence analysis, large case / control studies

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.

Classification of IARC Class 3 Variants

Requires additional information and analyses, e.g.

- **Co-occurence 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).**

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 critiera 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 valide 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)

Non-Directive Counseling Regarding Preventive Measures

AGO ++

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

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

Allow appropriate time for consideration

Multimodal Intensive Surveillance Program*

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

* The multimodal early detection program should be carried out for women with a pathogenic mutation in risk genes and those with an increased calculated risk without a mutation within the framework of transparent quality assurance and appropriate evaluation

High-Risk Breast Cancer Surveillance with MRI

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

PPV: Positive predictive value

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

Bick U, Engel C, Krug B, et al. High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer. *Breast Cancer Res Treat*. 2019;175(1):217–228. doi:10.1007/s10549-019-05152-9

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

			Oxford		
			LoE	GR	AGO
Multimodal intensive surveillance program°					
For detection of early stage breast cancers			**2a**	**B**	**++**
Clinical breast exam	≥ 25 years*	Semi-annually			
Sonographie	≥ 25 years*	Semi-annually			
Mammogram	≥ 40 years*	Biannually			
Breast MRI (until ACR1)	≥ 25 years*	Annually			
For mortality reduction (10-year survival)			**3a**	**C**	**+/-***

° Aftercare should be carried out within the framework of transparent quality assurance and corresponding evaluation.

* or from age at initial diagnosis

Surveillance for Male Carriers of Pathogenic BRCA Mutations*

The lifetime risk of breast cancer in the general male population is 0.1 %. *BRCA1* mutation carriers have a risk of breast cancer of about 1 % and an up to 1.8 to 3.75 times higher risk for prostatic cancer ≤ 65y.

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

	Oxford		
	LoE	GR	AGO

Currently, no specific surveillance is recommended →
Early detection of cancer as part of standard care

	LoE	GR	AGO
▪ For breast cancer: self examination	5	D	+
▪ For prostate cancer: Compare German Guideline program	5	D	+

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

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.**

Surgical Prevention

	Oxford		
	LoE	GR	AGO
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.	2a	B	+*

* study participation recommended

Surgical Prevention for <u>Healthy</u> Female *BRCA1/2* Mutation Carriers

	Oxford		
	LoE	**GR**	**AGO**
▪ **Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)****	**2a**	**B**	
▪ **Reduces OvCa incidence and mortality**			**++***
▪ **Reduces overall mortality**			**++***
▪ **Risk-reducing bilateral mastectomy (RR-BM)**			
▪ **Reduces BC incidence**	**2b**	**B**	**+***
▪ **Reduces BC mortality in *BRCA1* mutation carriers*****	**2b**	**B**	**+***

*   **Study participation recommended**
**   **The 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.**

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

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

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

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.

Therapy of Germline Mutation-Associated Breast Cancer

	Oxford		
Limited prospective cohort studies with short follow-up time	**LoE**	**GR**	**AGO**
▪ **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 (Her2-negative carcinomas):			
▪ **EBC: Olaparib (in case of *gBRCA1/2* mutation)***	**1b**	**B**	**+**
▪ **MBC:**			
gBRCA1/2 mutation			
Olaparib	**1b**	**A**	**++**
Talazoparib	**1b**	**A**	**++**
• **Somatic *BRCA1/2* mutation (germline testing is standard)**			
Olaparib	**2b**	**B**	**+/-**
• **_gPALB2_**			
Olaparib	**2b**	**B**	**+/-**

EBC: Early Breast Cancer; MBC: Metastatic Breast Cancer; * Use according to study inclusion criteria and approval

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	+**

* 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.

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

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Guidelines Breast
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FORSCHEN
LEHREN
HEILEN

Check list (inclusion criteria)
Counseling for diagnostic genetic testing

Certified BC Center

Communication, Exchange, Advice

Genetic testing

Familial BC Center

Prophylactic surgery
Stratified therapy

Counseling: Indication for surveillance and / or prophylatic surgery

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