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Breast Cancer Risk and Prevention

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

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

Principles of Prevention

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

(Primum nil nocere)

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

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

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. (before the 51st birthday) 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 before the 51st birthday
- at least one woman affected by breast cancer < 35 yrs. (before the 36th birthday) or
- at least one man affected by breast cancer and one additional relative affected by breast or ovarian cancer

* 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).

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

(Part 2 of 2 - testing according to disease)

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)**

* **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).**

AGO
ARBEITSGEMEINSCHAFT GYNÄKOLOGISCHE ONKOLOGIE E.V.
KOMMISSION MAMMA

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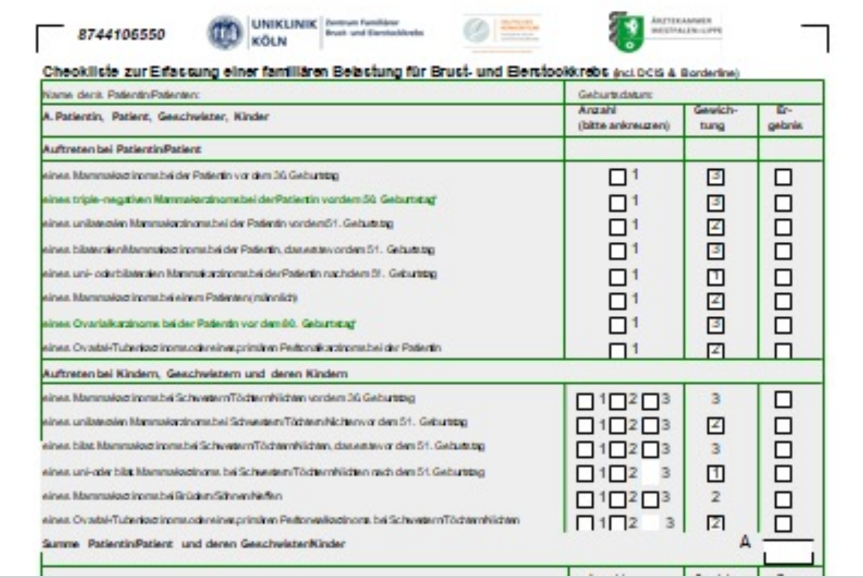
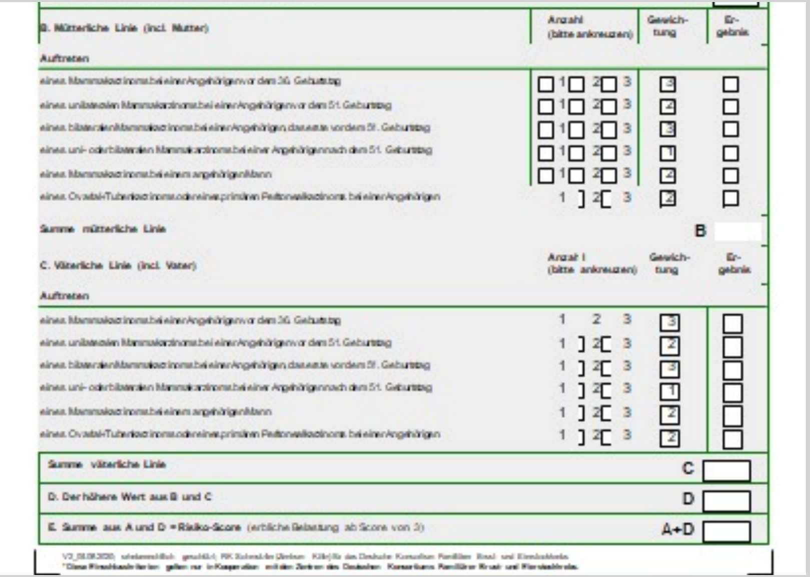
Checklist according to Public Health Insurance Policies (German GKV)



8744106550 UNIKLINIK KÖLN

Checkliste zur Erfassung einer familiären Belastung für Brust- und Eierstockkrebs (incl. DCIS & Borderline)

Name der/s Patientin/Patienten:	Geburtsdatum:		
A. Patientin, Patient, Geschwister, Kinder	Anzahl (bitte ankreuzen)	Gewichtung	Ergebnis
Auftreten bei Patientin/Patient			
eines Mammakarzinoms bei der Patientin vor dem 36. Geburtstag	☐ 1	3	☐
eines triple-negativen Mammakarzinoms bei der Patientin vor dem 50. Geburtstag*	☐ 1	3	☐
eines unilateralen Mammakarzinoms bei der Patientin vor dem 51. Geburtstag	☐ 1	2	☐
eines bilateralen Mammakarzinoms bei der Patientin, das erste vor dem 51. Geburtstag	☐ 1	3	☐
eines uni- oder bilateralen Mammakarzinoms bei der Patientin nach dem 51. Geburtstag	☐ 1	1	☐
eines Mammakarzinoms bei einem Patienten (männlich)	☐ 1	2	☐
eines Ovarialkarzinoms bei der Patientin vor dem 80. Geburtstag*	☐ 1	3	☐
eines Ovarial-/Tubenkarzinoms oder eines primären Peritonealkarzinoms bei der Patientin	☐ 1	2	☐
Auftreten bei Kindern, Geschwistern und deren Kindern			
eines Mammakarzinoms bei Schwestern/Töchtern/Nichten vor dem 36. Geburtstag	☐ 1 ☐ 2 ☐ 3	3	☐
eines unilateralen Mammakarzinoms bei Schwestern/Töchtern/Nichten vor dem 51. Geburtstag	☐ 1 ☐ 2 ☐ 3	2	☐
eines bilat. Mammakarzinoms bei Schwestern/Töchtern/Nichten, das erste vor dem 51. Geburtstag	☐ 1 ☐ 2 ☐ 3	3	☐
eines uni- oder bilat. Mammakarzinoms bei Schwestern/Töchtern/Nichten nach dem 51. Geburtstag	☐ 1 ☐ 2 3	1	☐
eines Mammakarzinoms bei Brüdern/Söhnen/Neffen	☐ 1 ☐ 2 ☐ 3	2	☐
eines Ovarial-/Tubenkarzinoms oder eines primären Peritonealkarzinoms bei Schwestern/Töchtern/Nichten	☐ 1 ☐ 2 3	2	☐
Summe Patientin/Patient und deren Geschwister/Kinder			A



B. Mütterliche Linie (incl. Mutter)	Anzahl (bitte ankreuzen)	Gewichtung	Ergebnis
Auftreten			
eines Mammakarzinoms bei einer Angehörigen vor dem 36. Geburtstag	☐ 1 ☐ 2 ☐ 3	3	☐
eines unilateralen Mammakarzinoms bei einer Angehörigen vor dem 51. Geburtstag	☐ 1 ☐ 2 ☐ 3	2	☐
eines bilateralen Mammakarzinoms bei einer Angehörigen, das erste vor dem 51. Geburtstag	☐ 1 ☐ 2 ☐ 3	3	☐
eines uni- oder bilateralen Mammakarzinoms bei einer Angehörigen nach dem 51. Geburtstag	☐ 1 ☐ 2 ☐ 3	1	☐
eines Mammakarzinoms bei einem angehörigen Mann	☐ 1 ☐ 2 ☐ 3	2	☐
eines Ovarial-/Tubenkarzinoms oder eines primären Peritonealkarzinoms bei einer Angehörigen	1 2 3	2	☐
Summe mütterliche Linie			B

C. Väterliche Linie (incl. Vater)	Anzahl (bitte ankreuzen)	Gewichtung	Ergebnis
Auftreten			
eines Mammakarzinoms bei einer Angehörigen vor dem 36. Geburtstag	1 2 3	3	☐
eines unilateralen Mammakarzinoms bei einer Angehörigen vor dem 51. Geburtstag	1 2 3	2	☐
eines bilateralen Mammakarzinoms bei einer Angehörigen, das erste vor dem 51. Geburtstag	1 2 3	3	☐
eines uni- oder bilateralen Mammakarzinoms bei einer Angehörigen nach dem 51. Geburtstag	1 2 3	1	☐
eines Mammakarzinoms bei einem angehörigen Mann	1 2 3	2	☐
eines Ovarial-/Tubenkarzinoms oder eines primären Peritonealkarzinoms bei einer Angehörigen	1 2 3	2	☐
Summe väterliche Linie			C
D. Der höhere Wert aus B und C			D
E. Summe aus A und D = Risiko-Score (erbliche Belastung ab Score von 3)			A+D

online tool provided by the GC-HBOC , V2_05.08.2020
https://familiaerer-brust-und-eierstockkrebs.uk-koeln.de/informationen/downloads/

www.ago-online.de

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State of research: Relevance of genetic and non-genetic risk factors

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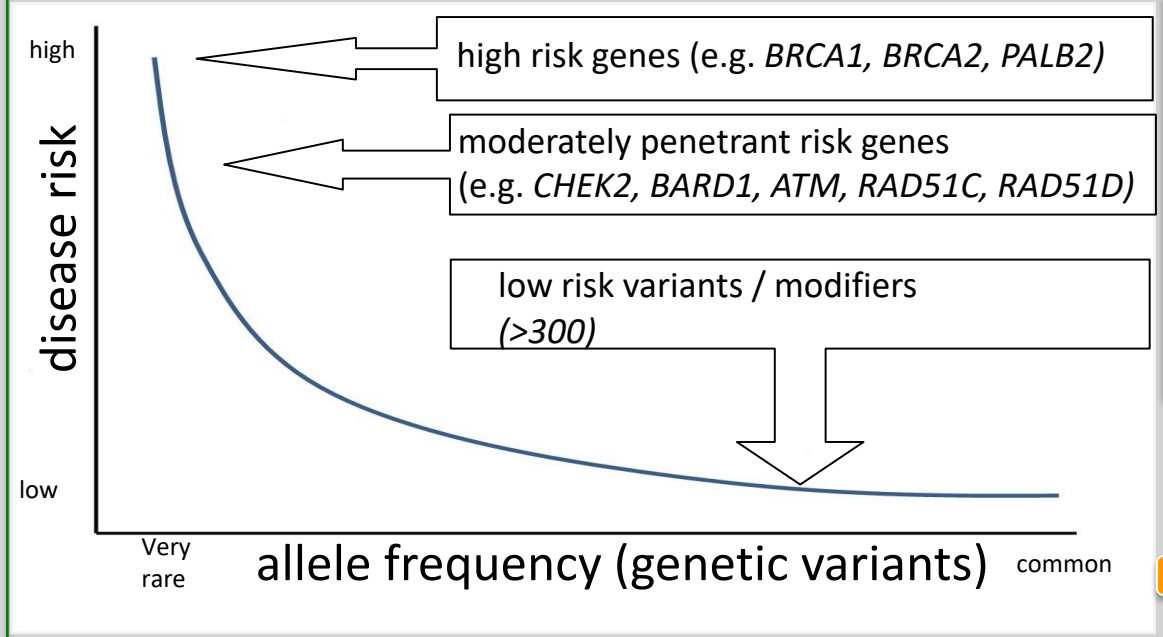

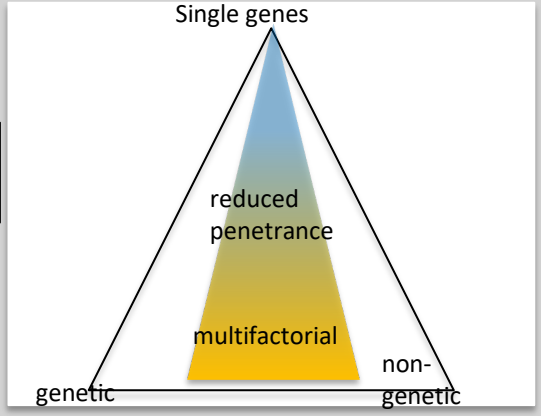

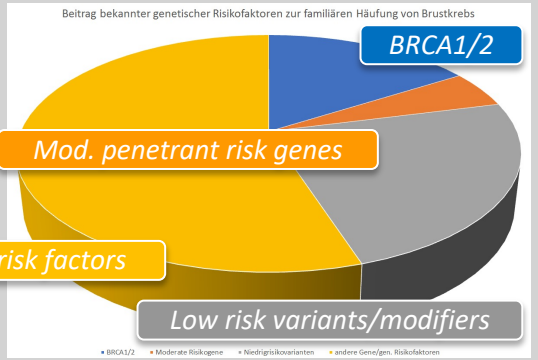

Genes with Moderate to High Lifetime Risk for Breast Cancer

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	Oxford		
	LoE	GR	AGO
Cumulative risk for breast cancer			
▪ high: ***BRCA1, BRCA2, PALB2***	1b	A	++
▪ moderate: ***ATM, CHEK2, BARD1, RAD51C, RAD51D***	1b	B	+
Clinical benefit* of a genetic test			
▪ ***BRCA1, BRCA2***	1b	A	++°
▪ ***PALB2***	3a	B	+°
▪ ***ATM, BARD1, CHEK2, RAD51C, RAD51D***	3a	B	+/-°

*** Efficacy of preventive strategies.**

° Participation in prospective registries or studies is highly recommended.

Estimated Cumulative Risk of Breast Cancer with Protein-Truncating Variants in 8 Genes

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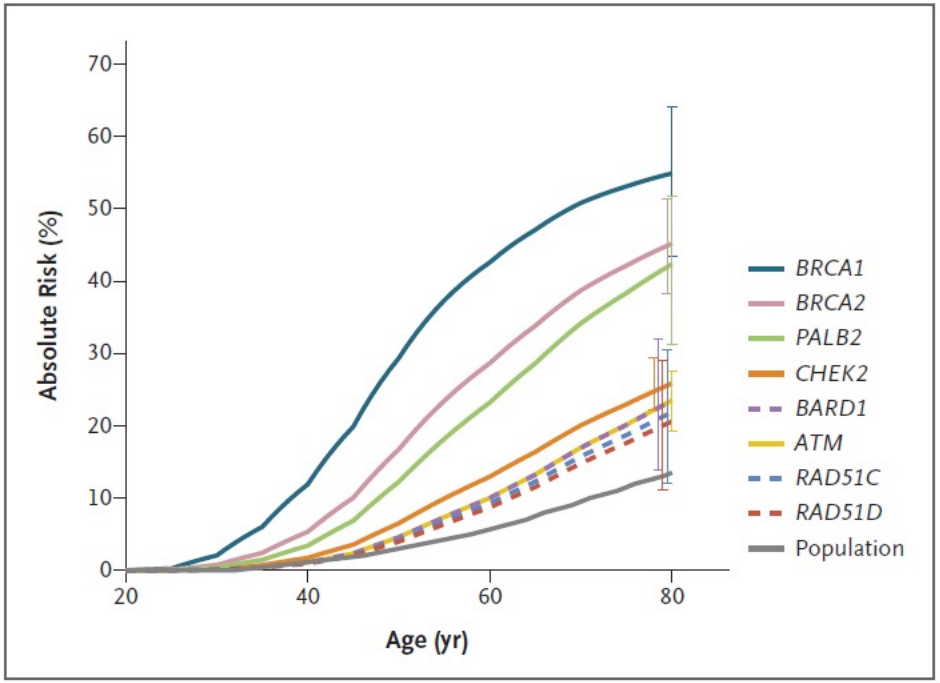

Shown are cumulative risks of breast cancer through 80 years of age for protein-truncating variants in 8 genes that had significant evidence of an association with breast cancer overall, on the basis of estimated odds ratios from population-based studies. Baseline absolute risks were derived from population 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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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, 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	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	+

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

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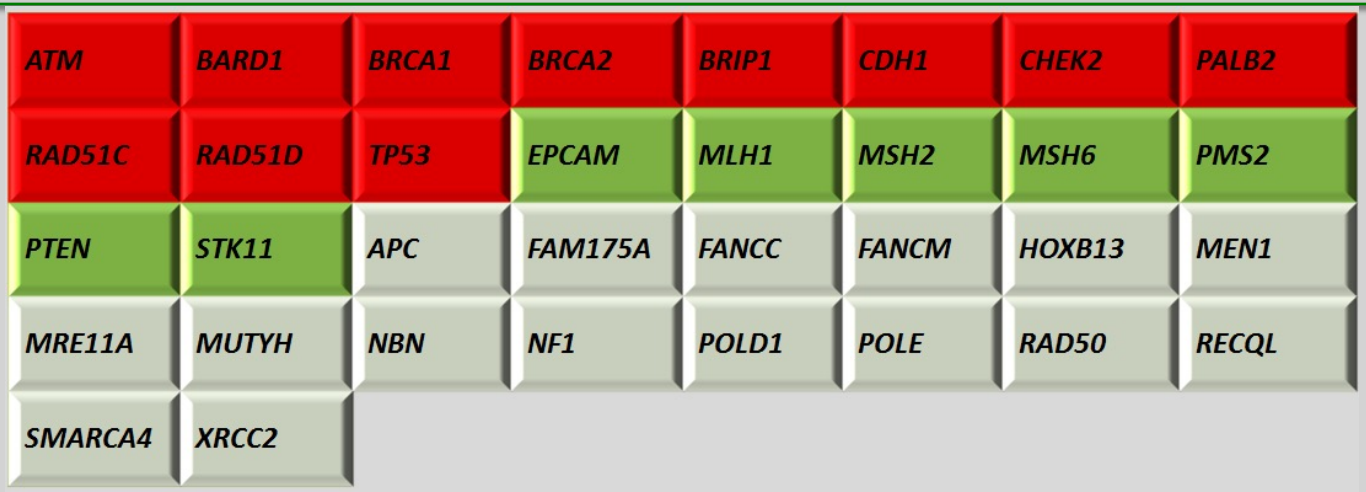
Syndrome	Gene	Risk for malignancy
Li Fraumeni	*TP53*	Breast, endometrium, colorectal, small intestine, stomach, hepato biliary, skin, osteosarcoma, soft tissue sarcoma, urogenital, CNS, ACC, leukemia, lymphoma, lung
Cowden	*PTEN*	breast, endometrium, thyroid, colorectal, kidney, melanoma
Hereditary diffuse 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)



Selection of genes:	**11 BC/OC '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	

*BC=breast cancer, oc=ovarian cancer

Distinct Genetically Subtypes Defines Distinct Tumor Entities

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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-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)

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Non-Directive Counseling regarding Preventive Measures

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Oxford		
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 women already affected by primary breast cancer
- Allow appropriate time for consideration

Multimodal Intensive Surveillance Program*

		Oxford LoE	Oxford GR	Oxford AGO
▪ Program für BRCA-Carriers				
▪ For the detection of early stage cancers		2b	B	++
▪ Clinical breast exam	> = 25 Jahre	Semi-annually		
▪ Sonography	> = 25 Jahre	Semi-annually		
▪ Mammogram	> = 40 Jahre	Bi-annually		
▪ Breast MRI	> = 25 Jahre	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 intensified early detection program should be carried out 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

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

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

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

Surveillance for male carriers of pathogenic BRCA Mutations*

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 </= 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			
▪ **For breast cancer: self examination and watchful waiting**	5	D	+
▪ **For prostate cancer: Compare German Guideline program**	5	D	+

*** 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

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

	Oxford LoE	Oxford 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

** 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. RRM counselling should be individualised.

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

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	Oxford		
	LoE	GR	AGO
▪ Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)	2b	B	+*
▪ Reduces OvCa incidence and mortality			
▪ Reduces overall mortality (contradictory results regarding reduction of contralateral 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 (≥ 5y), age

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

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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

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Limited prospective cohort studies with short follow-up time	Oxford 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 in metastatic breast cancer			
• BRCA1/2	1b	B	+
• PALB2	2b	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 regarding 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 #Tyrer-Cuzick model (IBIS-II)

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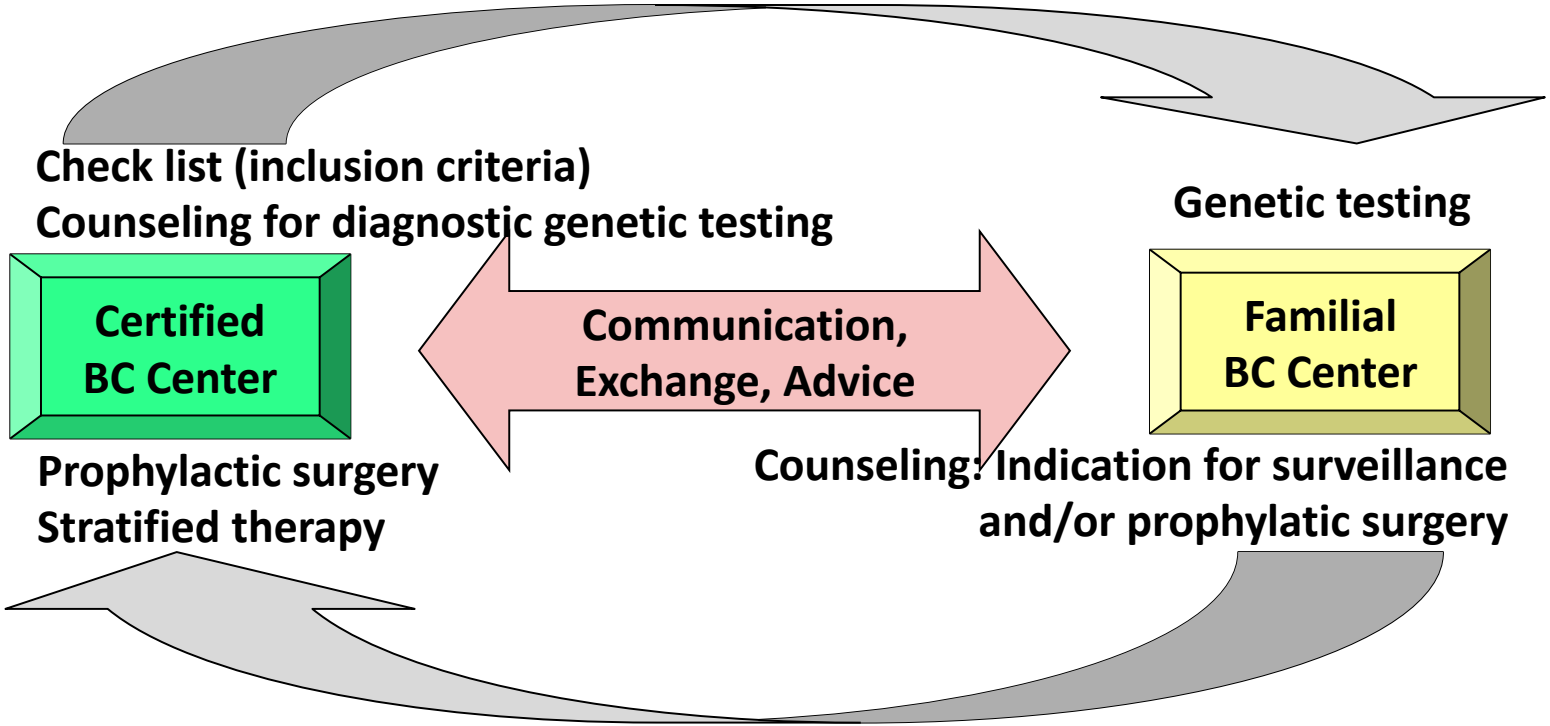
Risk Reduction for Ipsi- and Contralateral Breast Cancer

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

	Oxford		
	LoE	GR	AGO
▪ Tamoxifen*	1a	A	+
▪ Aromatase inhibitors*	1a	A	+
▪ Suppression of ovarian function* + Tamoxifen	1b	B	+

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

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

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