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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 2003–2018:**
Schmutzler with Albert / Blohmer / Fasching / Fehm / Kiechle / Maass / Mundhenke / Riehm / Rody / Schmidt / Stickeler / Thomssen
- **Version 2019:**
Ditsch / Müller-Schimpfle / Bischoff

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?

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

Families with*


- 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.
3. German Consortium for Hereditary Breast and Ovarian Cancer. Criteria for families in which the mutation probability exceeds 10%. . personal communication. 2016.
4. Hahnen E, Baumann KH, Heimbach A, et al. Prevalence of somatic mutations in risk genes including BRCA1/2 in consecutive ovarian cancer patients (AGO-TR-1 study). J Clin Oncol. 2016;34:(suppl; abstr 5544).
5. 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.
6. von Minckwitz G., E. Hahnen, P. A. Fasching, et al. Pathological complete response (pCR) rates after carboplatin-containing neoadjuvant chemotherapy in patients with germline BRCA (gBRCA) mutation and triple-negative breast cancer (TNBC): Results from GeparSixto. J Clin Oncol 2014;32:5s:(suppl; abstr 1005).
7. 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. - neu

8. 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 BCA-D-17-00805R2 (in revision) - neu
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
10. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation N Engl J Med 2017;377:523-533
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?

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

Families with*

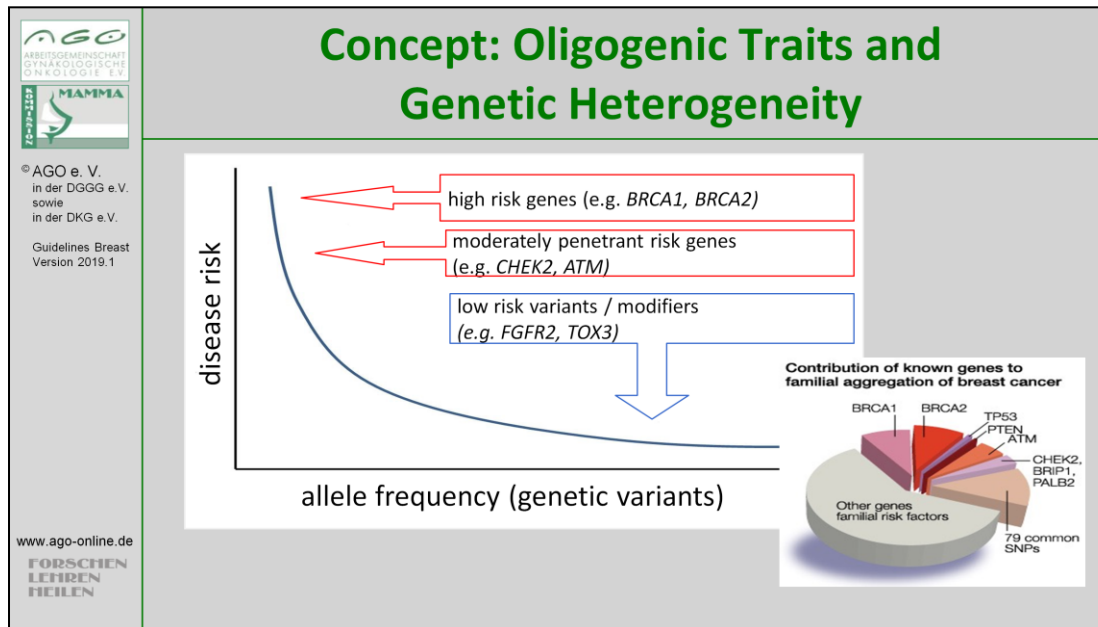
- at least one woman affected by breast cancer < 35 yrs. or
- at least one man affected by breast cancer and one additional relative affected by breast or ovarian cancer
- Inclusion criteria based on a mutation detection rate $\geq 10\%$ if women has already breast or ovarian cancer (without affected family members):
 - own disease of triple negative breast cancer ≤ 60 yrs. of age
 - own disease with ovarian cancer
 - if this information has therapeutical implication

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3. German Consortium for Hereditary Breast and Ovarian Cancer. Criteria for families in which the mutation probability exceeds 10%. . personal communication. 2016.
4. Hahnen E, Baumann KH, Heimbach A, et al. Prevalence of somatic mutations in risk genes including BRCA1/2 in consecutive ovarian cancer patients (AGO-TR-1 study). J Clin Oncol. 2016;34:(suppl; abstr 5544).
5. 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.
6. von Minckwitz G., E. Hahnen, P. A. Fasching, et al. Pathological complete response (pCR) rates after carboplatin-containing neoadjuvant chemotherapy in patients with germline BRCA (gBRCA) mutation and triple-negative breast cancer (TNBC): Results from GeparSixto. J Clin Oncol 2014;32:5s:(suppl; abstr 1005).
7. 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. - neu

8. 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 BCA-D-17-00805R2 (in revision) - 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).



1. Couch F, Shimelis H, Hu C, et al. Breast Cancer risks associated with mutations in cancer predisposition genes identified by clinical genetic testing of 60,000 breast cancer patients. San Antonio Breast Cancer Symposium. 2016:Abstract S2-01.
2. Couch FJ, Shimelis H, Hu C, et al. Associations between cancer predisposition testing panel genes and breast cancer JAMA Oncol 2017;3:1190-1196.
3. Couch FJ, Nathanson KL, Offit K. Two decades after BRCA: setting paradigms in personalized cancer care and prevention. Science. 2014;343(6178):1466-70.
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Breast Cancer Risk Genes with moderate to high Lifetime Risk


For following genes are risk calculations available with varying degrees of evidence.
The clinical benefit must be proven by the effectiveness of preventive measures.
OR from subgroups can not be transferred to other subgroups.

Clinical benefit of genetic test	Oxford		
	LoE	GR	AGO
▪ <i>BRCA1</i> (#), <i>BRCA2</i> *	1b	A	++ [°]
▪ <i>PALB2</i> (#), <i>CDH1</i> , <i>TP53</i> **	3a	C	+/- [°]
▪ <i>ATM</i> , <i>CHEK2</i> , <i>BARD1</i> (#), <i>BRIP1</i> , <i>MSH6</i> , <i>RAD51D</i> ***	3a	C	+/- [°]

* *BRCA1/2* are genes with a high lifetime risk. Furthermore genes with a medium and a low lifetime risk have been described.
** High OR 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 the 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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4. Couch F, Shimelis H, Hu C, et al. Breast Cancer risks associated with mutations in cancer predisposition genes identified by clinical genetic testing of 60,000 breast cancer patients. San Antonio Breast Cancer Symposium. 2016:Abstract S2-01.
5. Couch FJ, Nathanson KL, Offit K. Two decades after BRCA: setting paradigms in personalized cancer care and prevention. *Science*. 2014;343(6178):1466-70.
6. Hauke J, Horvath J, Groß E, et al. Gene panel testing of 5589 BRCA1/2-negative index patients with breast cancer in a routine diagnostic setting: results of the German Consortium for Hereditary Breast and Ovarian Cancer. *Cancer Med*. 2018 Mar 9. doi: 10.1002/cam4.1376. [Epub ahead of print]
7. Shimelis H, LaDuca, Hu C et al.: Triple-negative breast cancer risk genes identified by multigene hereditary cancer panel testing. *J*

Natl Cancer Inst 2018 Aug 7.doi:10.1093/jnci/djy106.



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Current Clinical Impact Further Risk Genes

- Further moderate and low-risk gene variants are most likely be transmitted by an oligo- or polygenic trait.
- The penetrance of such genes depends on family cancer history and own disease history.
- 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 the provision of clinical prevention strategies remain to be elucidated.
- 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
▪ <i>Clinical genetic testing of moderate risk genes, e.g. gene panels</i>	3a	B	+/-
▪ Clinical genetic testing for low risk variants	3b	D	--
▪ Referral to centres of the GC-HBOC or cooperating centres	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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4. Michailidou K, Hall P, Gonzalez-Neira A, et al. Large-scale genotyping identifies 41 new loci associated with breast cancer risk. Nat Genet. 2013;45(4):353-61.
5. Michailidou K, Beesley J, Lindstrom S, et al. Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. Nat Genet. 2015;47(4):373-80.
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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
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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4. Song H, Dicks E, Ramus SJ, et al. Contribution of Germline Mutations in the RAD51B, RAD51C, and RAD51D Genes to Ovarian Cancer in the Population. *J Clin Oncol*. 2015;33(26):2901-7.
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9. Tan MH, Mester JL, Ngeow J, et al. Lifetime cancer risks in individuals with germline PTEN mutations. *Clin Cancer Res.* 2012;18(2):400-7.
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14. Hauke J, Horvath J, Groß E, et al. Gene panel testing of 5589 BRCA1/2-negative index patients with breast cancer in a routine diagnostic setting: results of the German Consortium for Hereditary Breast and Ovarian Cancer. *Cancer Med.* 2018 Mar 9. doi: 10.1002/cam4.1376.



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Breast Cancer Gene Panels (e.g.)

BROCA gene panel

(cross-cancer. <http://web.la.med.washington.edu/tests/genetics/BROCA>)

AKT1
 ALK
 APC
 ATM
 ATR
 AXIN2
 BAP1
 BARD1
 BRCA1
 BRCA2
 BRIP1
 CDH1
 CDK4
 CDKN2A
 CHEK1
 CHEK2
 CTNNA1
 EPCAM
 FAM175A
 FANCM
 FH
 GALNT12
 GEN1
 GREM1
 HDX13
 KIF18
 MEN1
 MET
 MITF
 MLH1
 MRE11A
 MSH2+EPICAM
 MSH3
 MSH6
 MUTYH

NBN
 NF1
 NTHL1
 PALB2
 PALD
 PDGFRA
 PHOXB2
 PIK3CA
 PMS2
 POLD1
 POLE
 PRKAR1A
 PRSS1
 PTCH1
 PTEN
 RAD51B
 RAD51C
 RAD51D
 RB1
 RECQL
 RET
 RINT1
 RPS20
 SDHB
 SDHC
 SDHD
 SLK4
 SMAD4
 SMARCA4
 TP53
 TP53BP1
 VHL
 XRCC2

AMBR Genetics BreastNext

<http://www.ambrygen.com/tests/breastnext>

ATM
 BARD1
 BRCA1
 BRCA2
 BRIP1
 CDH1
 CHEK2
 MRE11A
 MUTYH
 NBN
 NF1
 PALB2
 PTEN
 RAD50
 RAD51C
 RAD51D
 TP53

CEGAT CANO2: Brust- und Ovarialkarzinom

http://www.cegat.de/Tumorerkrankungen_171.html

ATM
 BARD1
 APC
 BRCA1
 BRIP1
 CDH1
 CHEK2
 EPCAM
 FAM175A
 FANCA
 FANCC
 FANCD2
 FANCE
 FANCF
 FANGG
 HOXB13
 MEN1
 MLH1
 MRE11A
 MSH2
 MSH3
 MSH6
 MUTYH
 NBN
 NF1
 PALB2
 PMS2
 PTCH1
 PTEN
 RAD50
 RAD51C
 RAD51D
 RINT1
 SDHB
 SDHC
 SDHD
 SLK4
 STK11
 TP53
 XRCC2

TruSight™ Cancer (Illumina)

http://res.illumina.com/documents/products/56datasheets/56data-sheet_trusight_cancer.pdf

AIP
 ALK
 APC
 ATM
 BAP1
 BLM
 BMP1A
 BRCA1
 BRCA2
 BRIP1
 BUB1B
 CDC73
 CDH1
 CDK4
 CDKN1C
 CDKN2A
 CEP57
 CHEK2
 CYLD
 DDB2
 DICER1
 DUSP12
 EGFR
 EPCAM
 ERCC2
 ERCC3
 ERCC4
 ERCC5
 EXT1
 EXT2
 EZH2
 FANCA
 FANCB
 FANCC
 FANCD2
 FANCE
 FANCF

FANGG
 FANCI
 FANCL
 FANCM
 FH
 FLCN
 GATA2
 SMAD4
 SMARCB1
 STK11
 SUFU
 TMEM127
 TP53
 MAX
 MEN1
 MET
 MLH1
 MSH2
 MSH6
 MUTYH
 NBN
 NF1
 NF2
 NSD1
 PALB2
 PHOXB2
 PMS1
 PMS2
 PRF1
 PRKAR1A
 PTCH1
 PTEN
 RAD51C
 RAD51D
 RB1
 RECQL4
 RET
 RHBDF2
 RUNX1

SBOS
 SDHAF2
 SDHB
 SDHC
 SDHD
 SLK4
 SMAD4
 SMARCB1
 STK11
 SUFU
 TMEM127
 TP53
 TSC1
 TSC2
 VHL
 WRN
 WT1
 XPA
 XPC

CENTOGENE Breast

<https://www.centogene.com/centogene>

ATM
 BARD1
 BRCA1
 BRCA2
 BRIP1
 CDH1
 CHEK2
 NBN
 PALB2
 PTEN
 RAD51C
 STK11
 TP53

MYRIAD myRisk Panel

APC
 ATM
 BARD1
 BMP1A
 BRCA1
 BRCA2
 BRIP1
 CDH1
 CDK4
 CDKN2A
 CHEK2
 EPCAM
 GREM1
 MLH1
 MSH2
 MSH6
 MUTYH
 NBN
 PALB2
 PMS2
 POLD1
 POLE
 PTEN
 RAD51C
 RAD51D
 SMAD4
 STK11
 TP53

1. Kurian AW, Idos G, Culver J, et al. Safety of multiplex gene testing for inherited cancer risk: Interim analysis of a clinical trial. J Clin Oncol. 2016;34:(suppl; abstr 1503).

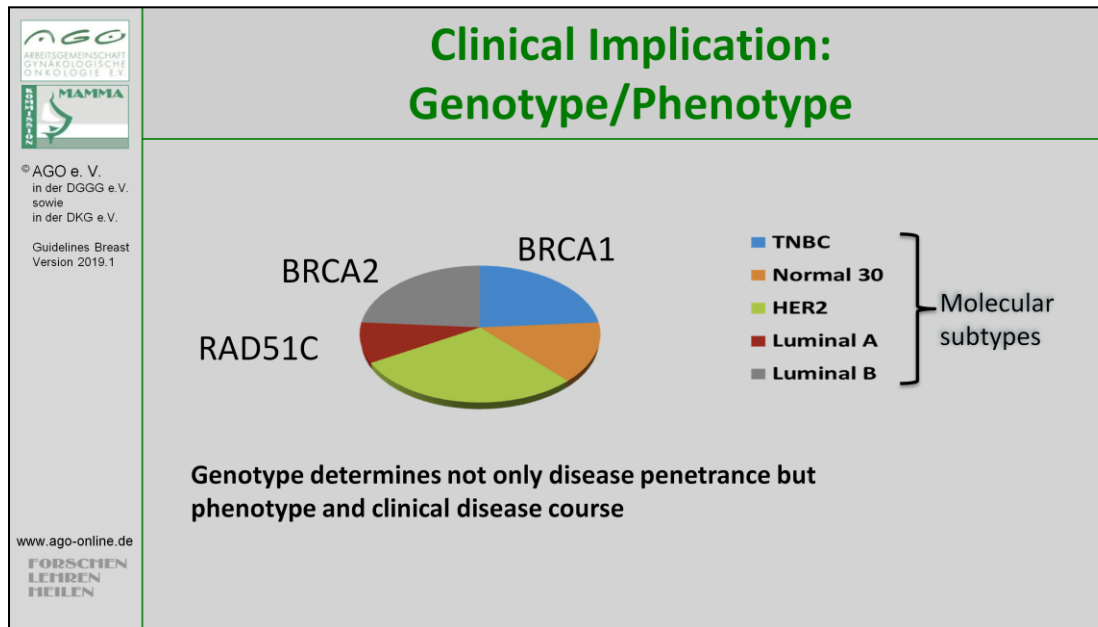
TruRisk® BC/OC Gene Panel (34 genes) by the German Consortium GC-HBOC

ATM	BRCA1	BRCA2	BRIP1	CDH1	CHEK2	PALB2	RAD51C
RAD51D	TP53	EPCAM	MLH1	MSH2	MSH6	PMS2	BARD1


Gene selection: **10 BC/OC ,core genes‘** (sufficient data for genetic counseling)
5 HNPCC genes
 further syndromic genes (Cowden, Peutz-Jeghers)
19 BC/OC genes as part of scientific validation

Strategy:

- Validation in large cohort, constant expansion and improvement



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2. 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.
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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

1. Plon SE, Eccles DM, Easton D, et al. Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. Human mutation. 2008;29(11):1282-91.
2. Ernst C, Hahnen E., Engel Ch, Nothnagel M, Weber J, Schmutzler RK, Hauke J. Performance of in silico prediction tools for the classification of rare BRCA1/2 missense variants in clinical diagnostics. BMC Medical Genomics.



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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 no of clinical significance	< 0,001

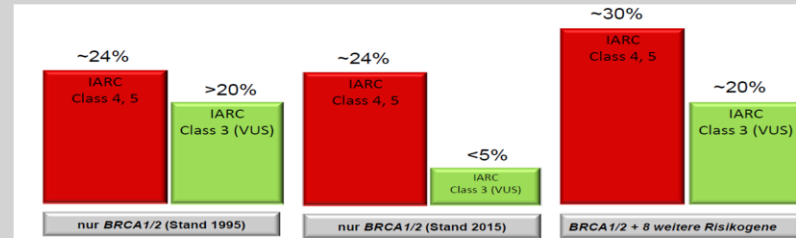
Only class 4 and 5 variants are considered clinically relevant.

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.

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.



Reduction of IARC class 3 classification in the German population due to scientific results of German consortium of hereditary breast and ovarian cancer (GC-HBOC)

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



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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
<http://www.bmg.bund.de/themen/praevention/nationaler-krebsplan/was-haben-wir-bisher-erreicht/querschnittsthema-risiko-adaptierte-krebsfrueherkennung.html>

1. Schmutzler RK, et al. Risikoadaptierte Früherkennung, Ein Papier der Unterarbeitsgruppe „Risikoadaptierte Früherkennung der AG1 „Weiterentwicklung der Krebsfrüherkennung“ des Nationalen Krebsplans.
http://www.bmg.bund.de/fileadmin/dateien/Downloads/N/Nationaler_Krebsplan/Zielepapier_zum_Querschnittsthema_Risiko-adaptierte_Krebsfrueherkennung.pdf. 2011.



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Non Directive Counseling for the Uptake of Preventive Measures

- 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 progressive disease in relation to the risk of a secondary primary in case women have already been affected by primary breast cancer
- Allow appropriate time for consideration

Oxford		
LoE	GR	AGO
5	D	++

1. 1Phi 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 Semi-annually ■ Sonographie (Intervall between MRI) > = 25 Jahre Annually ■ Mammogram > = 40 Jahre Bi-annually ■ Breast MRI > = 25 Jahre Annually ■ For reduction of metastasis free interval ■ Survivors after tumors in childhood and radiotherapy of thoracic wall (e.g. M. Hodgkin) 				
		2b	B	++
		2b	B	+
		2a	B	++

* 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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8. Ellen Warner: Screening BRCA1 and BRCA2 Mutation Carriers for Breast Cancer. Review. Cancers 2018, 10, 477;
doi:10.3390/cancers10120477
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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., Endel 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, accepted


High risk screening including MRI

Table 6. 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
BRCAl-carriers	2,760	83	26.6	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		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		21.7 to 37.1	86.4	76.5 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	30.6	16.6 to 55.2	90.9	62.3 to 98.4	93.7	90.5 to 96.9	33.3	19.2 to 61.2
BRCAD-carriers	1,724	53	27.8	21.1 to 36.7	90.6	79.7 to 96.9	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
BRCAT2/10m-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	19.8	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 96.4	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	7.6 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

Abbreviations: CI, confidence interval; PPV, positive predictive value

Bick U., Endel 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, accepted



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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
■ Multimodal intensive surveillance program lifelong				
■ For the detection of early stage breast cancers		2a	B	++
■ 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)		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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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 a 1,8 to 3,75 times higher risk for prostatic cancer ≤ 65 y.

BRCA 2 mutation carrier have a 5-7% lifetime risk for breast cancer and a 2,5 to 8,6 times higher risk for prostatic cancer ≤ 65 y.


	Oxford LoE	GR	AGO
Currently no specific surveillance is recommended			
▪ For breast cancer prevention: self examination and watchful waiting	5	D	+
▪ For prostate cancer prevention: study participation if available	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.
2. Kote-Jarai Z, Leongamornlert D, Saunders E, et al. BRCA2 is a moderate penetrance gene contributing to young-onset prostate cancer: implications for genetic testing in prostate cancer patients. Br J Cancer. 2011;105(8):1230-4.
3. Breast Cancer Linkage C. Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst. 1999;91(15):1310-6.
4. Thompson D, Easton DF, Breast Cancer Linkage C. Cancer Incidence in BRCA1 mutation carriers. J Natl Cancer Inst. 2002;94(18):1358-65.
5. Leongamornlert D, Mahmud N, Tymrakiewicz M, et al. Germline BRCA1 mutations increase prostate cancer risk. Br J Cancer. 2012;106(10):1697-701.
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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.
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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**

* 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.



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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 (RRSO) <ul style="list-style-type: none"> ■ Reduces BrCa incidence and mortality ■ Reduces OvCa incidence and mortality ■ Reduces overall mortality ■ Risk-reducing bilateral mastectomy (RRM) <ul style="list-style-type: none"> ■ Reduces BrCa incidence and mortality 	2c	B	+/-* ++* ++* +*
<p>RR-BSO is recommended after completion of family planning</p> <p>RR-BM revealed a high incidence of premalignant lesions</p> <p style="color: green;">* study participation recommended</p>			

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.
2. Hoogerbrugge N, Bult P, Bonenkamp JJ, et al. Numerous high-risk epithelial lesions in familial breast cancer. Eur J Cancer. 2006;42(15):2492-8.
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11. Heemskerk-Gerritsen BAM, Seynaeve C, van Asperen CJ, et al.: Breast Cancer Risk After Salpingo-Oophorectomy in Healthy BRCA1/2 Mutation Carriers: Revisiting the Evidence for Risk Reduction. *JNCI J Natl Cancer Inst* (2015) 107(5): djv033
12. Ye-Lei Xiao, Kang Wang, Qiang Liu, et al.: Risk Reduction and Survival Benefit of Risk-Reducing Salpingo-oophorectomy in Hereditary Breast Cancer: Meta-analysis and Systematic Review. *Clinical Breast Cancer*, Vol. 19, No. 1, e48-65



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

	Oxford		
	LoE	GR	AGO
▪ Risk-reducing bilateral salpingo-oophorectomy (RRSO)	2b	B	+*
▪ Reduces OvCa incidence and mortality			
▪ Reduces BrCa incidence and mortality			
▪ Reduces overall mortality (contradictory results for reduction of cl BrCa incidence)			
▪ Prophylactic contralateral mastectomy (RRCM)	2b	B	+*
▪ Reduces BrCa incidence and mortality			
▪ Tamoxifen (reduces cl BrCa incidence)	2b	B	+/-*
▪ Indication for RRM should consider age at onset of first breast cancer in affected gene	2a	B	++*
▪ RRM after ovarian cancer	4	C	+/-**
* study participation recommended			
** Depends on tumor stage (FIGO I/II), recurrence free intervals (≥ 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 2019.1</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 +
	■ gBRCA1 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	A +

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SABCS:

Robson - OlympiAD

Litton SABCS - EMBRACA



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Medical Prevention for Women at Increased Risk

	Oxford LoE	GR	AGO
■ Tamoxifen for women >35 years reduction of invasive BrCa, DCIS, and LN	1a	A	+*
■ Raloxifen for postmenopausal women reduction of invasive BrCa 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)

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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

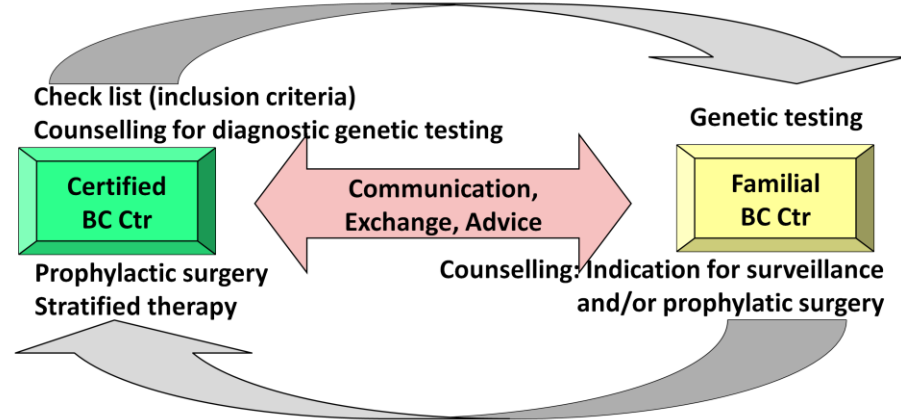
- Tamoxifen*
- Aromatasehemmer*
- Suppression of ovarian function* + Tamoxifen

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

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

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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