Breast Cancer Risk and Prevention
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- **Versions 2003–2017:**
  Schmutzler / Albert / Blohmer / Fasching / Fehm / Kiechle / Maass / Mundhenke / Rody / Schmidt / Stickeler / Thomssen

- **Version 2018:**
  Rhiem / Blohmer
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)
Who Should be Tested for BRCA1/2 Mutations and Possibly Further Risk Genes?

Families with*

- at least three women with breast cancer independent of age or
- at least two women with breast cancer, one < 51 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 < 51 yrs. or
- at least one woman affected by breast cancer < 36 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 ≥ 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

* 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
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), http://www.aekwl.de/fileadmin/qualitaetssicherung/Zertifizierungsstelle/FB-erbliche_Belastung_V2016-01-06.pdf
Concept: Oligogenic Traits and Genetic Heterogeneity

- high risk genes (e.g. BRCA1, BRCA2)
- moderately penetrant risk genes (e.g. CHEK2, ATM)
- low risk variants / modifiers (e.g. FGFR2, TOX3)
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

<table>
<thead>
<tr>
<th>Gene(s)</th>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA1, BRCA2</strong></td>
<td>2a/1b</td>
<td>A</td>
<td></td>
<td>++°</td>
</tr>
<tr>
<td><strong>PALB2, CDH1, TP53</strong></td>
<td>3a</td>
<td>C</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td><strong>ATM, CHEK2, BARD1, BRIP1, MSH6, RAD51D</strong></td>
<td>3a</td>
<td>C</td>
<td>+/-</td>
<td>-</td>
</tr>
</tbody>
</table>

* 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.
° Participation in prospective registries or studies is highly recommended.
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.
- Moderate risk genes exhibit very low mutation detection rates and may be associated with specific tumor subtypes.
- 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.

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<thead>
<tr>
<th>Oxford LoE</th>
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<th>AGO</th>
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<tbody>
<tr>
<td>3a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>3b</td>
<td>D</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
</tbody>
</table>

Clinical genetic testing of moderate risk genes, e.g. gene panels
Clinical genetic testing for low risk variants
Referral to centres of the GC-HBOC or cooperating centres
Non BRCA-associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer

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

AKT1
APC
ATM
ATR
AXIN2
BAP1
BARD1
BMPR1A
BRCA1
BRCA2
BRI1
CDH1
CDK4
CDKN2A
CHEK1
CHEK2
CTNNA1
EPCAM
FAM175A
FANCM
FH
GALNT12
GEN1
GREM1
HOXB13
MEN1
MET
MIF
MLH1
MRE11A
MSH2
MSH6
MUTYH
NBN
NF1
NTHL1
PALB2
PALLD
PDGFRA
PIK3CA
PMS2
POLD1
POLE
POT1
PRKAR1A
PRSS1
PTCH1
PTEN
RAD51B
RAD51C
RAD51D
RB1
RECQL
RET
RINT1
RPS20
SDHB
SDHC
SDHD
SLX4
SMAD4
SMARCA4
TP53
TP53BP1
VHL
XRCC2

ATM
BARD1
BRCA1
BRCA2
BRI1
CDH1
CHEK2
MRE11A
MUTYH
NBN
NF1
PALB2
PTEN
RAD50
RAD51C
RAD51D
TP53

AIP
ALK
APC
ATM
BAP1
BLM
BMPR1A
BRCA1
BRCA2
BRIP1
BUB1B
CDC73
CDH1
CDK4
CDKN1C
CDkn2A
CEBPA
CEP57
CHEK2
CYLD
DDB2
DICER1
DIS3L2
EGFR
EPCAM
ERCC1
ERCC2
ERCC3
ERCC4
ERCC5
EXT1
EXT2
EHZ2
FANCA
FANCB
FANCC
FANCD2
FANCE
FANCF
FANCN
FANCQ
FANCI
FANCL
FANCQ
FANCQ
FANCQ
FH
FLCN
GATA2
GAPDH
GPC3
HNF1A

HRAS
KIT
MAX
MEN1
MET
MLH1
MSH2
MSH6
MUTYH
NBN
NF1
NF2
NSD1
PALB2
PHOX2B
PMS1
PMS2
PRF1
PRKAR1A
PTCH1
PTEN
RAD51C
RAD51D
RHBDF2
RUNX1
SBDS
SDHAF2
SDHB
SDHC
SDHD
SLX4
SMAD4
SMARCB1
STK11
SUFI
TMEM127
TP53
TSC1
TSC2
VHL
WRN
WT1
XPA
XPC

http://www.ago-online.de

Guidelines Breast
Version 2018.1

www.ago-online.de
TruRisk® BC/OC Gene Panel (34 genes) by the German Consortium GC-HBOC

<table>
<thead>
<tr>
<th>ATM</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>BRIP1</th>
<th>CDH1</th>
<th>CHEK2</th>
<th>PALB2</th>
<th>RAD51C</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAD51D</td>
<td>TP53</td>
<td>EPCAM</td>
<td>MLH1</td>
<td>MSH2</td>
<td>MSH6</td>
<td>PMS2</td>
<td>BARD1</td>
</tr>
</tbody>
</table>

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
Clinical Implication: Genotype/Phenotype

Genotype determines not only disease penetrance but phenotype and clinical disease course.
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 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
Variant classification proposed by IARC
(Plon et al., Human Mutation, 2008)

Proposed Classification System for Sequence Variants Identified by Genetic Testing

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Probability of being pathogenic</th>
</tr>
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<tbody>
<tr>
<td>5</td>
<td>Definitely pathogenic</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>4</td>
<td>Likely pathogenic</td>
<td>0.95 – 0.99</td>
</tr>
<tr>
<td>3</td>
<td>Uncertain</td>
<td>0.05 – 0.949</td>
</tr>
<tr>
<td>2</td>
<td>Likely not pathogenic or of little clinical significance</td>
<td>0.001 – 0.049</td>
</tr>
<tr>
<td>1</td>
<td>Not pathogenic or no of clinical significance</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Only class 4 and 5 variants are considered clinically relevant.
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.

To be accumulated by large study groups such as ENIGMA

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)
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
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
Multimodal Intensive Surveillance Program*

- **Program für BRCA-Carriers**
  - For the detection of early stage cancers
    - Clinical breast exam \( \geq 25 \text{ Jahre} \)
    - Sonographie (Intervall between MRI) \( \geq 25 \text{ Jahre} \)
    - Mammogram \( \geq 40 \text{ Jahre} \)
    - Breast MRI \( \geq 25 \text{ Jahre} \)

- For reduction of metastasis free interval
  - Survivors after tumors in childhood and radiotherapy of thoracic wall (e.g. M. Hodgkin)

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<td></td>
<td>2b</td>
<td>B</td>
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* Early detection / screening should be performed within structured and quality assured programmes, that capture performance and outcome of early detection / screening measures.
Surveillance Program for Female Carriers of Pathogenic BRCA Mutations after Primary Breast Cancer acc. to GC-HBOC *

- Multimodal intensive surveillance program lifelong
  - For the detection of early stage breast cancers
    - Clinical breast exam >= 25 Jahre
    - Sonographie >= 25 Jahre
    - Mammogram >= 40 Jahre
    - Breast MRI (until ACR1) >= 25 Jahre
  - For mortality reduction (10 year survival)

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<td>2a</td>
<td>B</td>
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Follow up care / surveillance should be performed within structured and quality assured programmes, that capture performance and outcome of early detection / screening measures.
Breast Cancer Risk Genes with moderate to high Lifetime Risk

BRCA1 mutation carrier have a nearly normal risk for breast cancer (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 ≤ 65y.

Currently no specific surveillance is recommended

- For breast cancer prevention: self examination and watchful waiting
- For prostate cancer prevention: study participation if available

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<tr>
<td></td>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>3b</td>
<td>C</td>
<td>+</td>
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</tbody>
</table>

* Follow up care / surveillance should be performed within structured and quality assured programmes, that capture performance and outcome of early detection / screening measures
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
Unilateral or bilateral mastectomy is not indicated in the absence of clearly defined genetic risk factors.
Surgical Prevention for Healthy Female BRCA1/2 Mutation Carriers

- **Risk-reducing bilateral salpingo-oophorectomy (RR-PBSO, PBSO)** around 40 years of age
  - Reduces OvCa incidence and mortality
  - Reduces BrCa incidence and mortality
  - Reduces overall mortality

- **Prophylactic bilateral mastectomy (RR-BM, PBM)**
  - Reduces BrCa incidence and mortality

**Oxford**

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<thead>
<tr>
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<tr>
<td>2c</td>
<td>B</td>
<td>++*</td>
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RR-BSO is recommended after completion of family planning

RR-BM revealed a high incidence of premalignant lesions

* study participation recommended
Risk-reducing Interventions for BRCA1/2 Female Mutation Carriers Affected by Breast Cancer

- Risk-reducing bilateral salpingo-oophorectomy (RR-PBSO, PBSO)
  - Reduces OvCa incidence and mortality
  - Reduces BrCa incidence and mortality
  - Reduces overall mortality (contradictory results for reduction of cl BrCa incidence)

- Prophylactic contalateral mastectomy (RR-BM, PBM)
  - Reduces BrCa incidence and mortality

- Tamoxifen (reduces cl BrCa incidence)

- Indication for PBM should consider age at onset of first breast cancer in affected gene

- Prophylactic bilateral mastectomy after ovarian cancer

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<tbody>
<tr>
<td>2b</td>
<td>B</td>
<td></td>
<td>+*</td>
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<tr>
<td>2b</td>
<td>B</td>
<td></td>
<td>+*</td>
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<td>2b</td>
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<td>+/-*</td>
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<tr>
<td>2a</td>
<td>B</td>
<td></td>
<td>++*</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td></td>
<td>+/-**</td>
</tr>
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* study participation recommended
** Depends on tumor stage (FIGO I/II), recurrence free intervals (≥ 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.

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, Hooning MJ, Seynaeve C.


See table 3: Efficacy of contralateral risk-reducing mastectomy on overall survival

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 \textit{BRCA1/2}-associated Breast Cancer

Limited prospective cohort studies with short follow-up time

- Breast converging surgery: adequate local tumor control (~10 years observation)
- Systemic therapy according to sporadic breast cancer
- gBRCA1 mutation status is predictive for chemotherapy response in TNBC
- Carboplatin (vs. Docetaxel) in metastatic breast cancer
- PARP inhibitor in metastatic breast cancer

+ prognosis must be taken into account
Medical Prevention for Women at Increased Risk

- Tamoxifen for women >35 years reduction of invasive BrCa, DCIS, and LN
- Raloxifen for postmenopausal women reduction of invasive BrCa only
- AI for postmenopausal women

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<th>Oxford</th>
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<th>GR</th>
<th>AGO</th>
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<tbody>
<tr>
<td>1a</td>
<td>A</td>
<td>A+</td>
<td>+*</td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
<td>A+</td>
<td>+*</td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
<td>A+</td>
<td>+#</td>
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* Risk situation as defined in NSABP P1-trial (1.66% in 5 years)

# 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 Reduction for Ipsi- and Contralateral Breast Cancer

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

- Tamoxifen*  
  Oxford LoE: 1a, GR: A, AGO: +

- Aromatasehemmer*  
  Oxford LoE: 1a, GR: A, AGO: +

- Suppression of ovarian function* + Tamoxifen  
  Oxford LoE: 1b, GR: B, AGO: +

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