Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Breast Cancer Risk and Prevention
Breast Cancer Risk and Prevention

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

online tool provided by the GC-HBOC, V2_05.08.2020
https://familiaerer-brust-und-eierstockkrebs.uk-koeln.de/informationen/downloads
State of research: Relevance of genetic and non-genetic risk factors

- High risk genes (e.g. BRCA1, BRCA2, PALB2)
- Moderately penetrant risk genes (e.g. CHEK2, BARD1, ATM, RAD51C, RAD51D)
- Low risk variants / modifiers (>300)
- Single genes
- Reduced penetrance
- Multifactorial
- Non-genetic
- BRCA1/2
- Mod. penetrant risk genes
- Other genes/genet. risk factors
- Low risk variants/modifiers

Breast Cancer Risk and Prevention
## Genes with Moderate to High Lifetime Risk for Breast Cancer

### Cumulative risk for breast cancer

- **High:** *BRCA1, BRCA2, PALB2*
  - LoE: 1b
  - GR: A
  - AGO: ++

- **Moderate:** *ATM, CHEK2, BARD1, RAD51C, RAD51D*
  - LoE: 1b
  - GR: B
  - AGO: +

### Clinical benefit* of a genetic test

- **BRCA1, BRCA2**
  - LoE: 1b
  - GR: A
  - AGO: ++°

- **PALB2**
  - LoE: 3a
  - GR: B
  - AGO: +°

- **ATM, BARD1, CHEK2, RAD51C, RAD51D**
  - LoE: 3a
  - GR: B
  - AGO: +/-°

* 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

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.

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).

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical genetic testing of moderate-risk genes, e.g. gene panels</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Clinical genetic testing for low-risk variants (polygenic risk score)</td>
<td>2b</td>
<td>B</td>
<td>+/-*</td>
</tr>
<tr>
<td>Referral to centers of the GC-HBOC or cooperating centers</td>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
</tbody>
</table>
## 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>
</tbody>
</table>
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 **syndrome-associated genes** (Lynch, Cowden, Peutz-Jeghers) with suspected BC/OC association
- **16 BC/OC candidate genes** from scientific projects (validation in the GC-HBOC)

**Strategy:** Validation in prospective cohort, continuous expansion and improvement

*BC=breast cancer, oc=ovarian cancer*
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)

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Probability of being pathogenic</th>
</tr>
</thead>
<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 of no 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.
- 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 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.

Non-Directive Counseling regarding 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 disease progression in relation to risk of a secondary primary in women already affected by primary breast cancer
- Allow appropriate time for consideration

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<tr>
<td></td>
<td>5</td>
<td>D</td>
<td>++</td>
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</tbody>
</table>

Breast Cancer Risk and Prevention
Multimodal Intensive Surveillance Program*

- **Program für BRCA-Carriers**
- **For the detection of early stage cancers**
  - Clinical breast exam \( \geq 25 \text{ Jahre} \)
    - Semi-annually
  - Sonography \( \geq 25 \text{ Jahre} \)
    - Semi-annually
  - Mammogram \( \geq 40 \text{ Jahre} \)
    - Bi-annually
  - Breast MRI \( \geq 25 \text{ Jahre} \)
    - Annually
- **For improvement of metastasis-free interval**
- **Survivors after tumors in childhood and radiotherapy of thoracic wall (e.g. M. Hodgkin)**

\[
\begin{array}{c|c|c|c}
\text{LoE} & \text{GR} & \text{AGO} \\
2b & B & ++ \\
\end{array}
\]

* 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

<table>
<thead>
<tr>
<th>Detection rate (‰)</th>
<th>PPV (%)</th>
<th>Detection rate (‰)</th>
<th>PPV (%)</th>
<th>Detection rate (‰)</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>43.2</td>
<td>29.4</td>
<td>21.8</td>
<td>25.5</td>
<td>30.5</td>
</tr>
<tr>
<td>BRCA2</td>
<td>22.7</td>
<td>23.3</td>
<td>24.3</td>
<td>27.5</td>
<td>16.3</td>
</tr>
<tr>
<td>BRCA1/2-non carriers with high risk</td>
<td>2.9</td>
<td>2.8</td>
<td>7.4</td>
<td>6.8</td>
<td>10.9</td>
</tr>
</tbody>
</table>

PPV: Positive predictive value

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

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

- **Multimodal intensive lifelong surveillance program**
  - **For detection of early stage breast cancers**
    - Clinical breast exam: \( \geq 25 \) Jahre, Semi-annually
    - Sonography: \( \geq 25 \) Jahre, Semi-annually
    - Mammogram: \( \geq 40 \) Jahre, Biannually
    - Breast MRI (until ACR1): \( \geq 25 \) 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.

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<th>AGO</th>
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<tbody>
<tr>
<td></td>
<td>2a</td>
<td>B</td>
<td>++</td>
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</table>

* 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 \(\leq 65\)y.

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

Currently, no specific surveillance is recommended

- For breast cancer:
  - self examination and watchful waiting

- For prostate cancer:
  - Compare German Guideline program

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

* study participation recommended
Surgical Prevention for Healthy Female *BRCA1/2* Mutation Carriers

- **Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)**
  - Reduces OvCa incidence and mortality
  - Reduces overall mortality

- **Risk-reducing bilateral mastectomy (RR-BM)**
  - Reduces BC incidence
  - Reduces BC mortality in *BRCA1* mutation carriers

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>2a</td>
<td>B</td>
<td></td>
<td>*</td>
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<td></td>
<td></td>
<td></td>
<td>+++*</td>
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<tr>
<td></td>
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<td>+++*</td>
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<tr>
<td>2b</td>
<td>B</td>
<td></td>
<td>+*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+*</td>
</tr>
</tbody>
</table>

* 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

- Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)
  - Reduces OvCa incidence and mortality
  - Reduces overall mortality
    (contradictory results regarding reduction of contralateral BC incidence)

- Prophylactic contralateral mastectomy (RR-CM)*
  - Reduces BC incidence and mortality

- Tamoxifen (reduces contralateral BC incidence)

- 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.**

<table>
<thead>
<tr>
<th>Analysis&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Group</th>
<th>Person years of observation</th>
<th>Deaths</th>
<th>Mortality&lt;sup&gt;b&lt;/sup&gt; (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>Surveillance</td>
<td>3007</td>
<td>65</td>
<td>21.6 (16.9-27.6)</td>
<td>Ref</td>
</tr>
<tr>
<td></td>
<td>CRRM</td>
<td>1975</td>
<td>19</td>
<td>9.6 (6.1-15.1)</td>
<td>0.43 (0.26-0.72)&lt;sup&gt;c&lt;/sup&gt; 0.49 (0.29-0.82)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>(b)</td>
<td>Surveillance</td>
<td>2673</td>
<td>56</td>
<td>21.0 (16.1-27.2)</td>
<td>Ref</td>
</tr>
<tr>
<td></td>
<td>CRRM</td>
<td>1837</td>
<td>18</td>
<td>9.8 (6.2-15.5)</td>
<td>0.46 (0.27-0.79)&lt;sup&gt;c&lt;/sup&gt; 0.55 (0.32-0.95)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> 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).

<sup>b</sup> Per 1000 person years of observation.

<sup>c</sup> Univariate analysis.

<sup>d</sup> 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

Limited prospective cohort studies with short follow-up time

- Breast conserving surgery: adequate local tumor control (~10 years observation)  
  - LoE: 2a  
  - GR: B  
  - AGO: +

- Systemic therapy according to sporadic breast cancer  
  - LoE: 3a  
  - GR: B  
  - AGO: +

- gBRCA mutation status is predictive for chemotherapy response in TNBC  
  - LoE: 2b  
  - GR: B  
  - AGO: +

- Carboplatin (vs. Docetaxel) in metastatic breast cancer  
  - LoE: 2b  
  - GR: B  
  - AGO: +

- PARP inhibitor in metastatic breast cancer  
  - BRCA1/2  
  - LoE: 1b  
  - GR: B  
  - AGO: +
  - PALB2  
  - LoE: 2b  
  - GR: B  
  - AGO: +/-
Medical Prevention for Women at Increased Risk

- **Tamoxifen for women >35 years**: reduction of invasive BC, DCIS, and LN
  - Oxford: 1a A +*
- **Raloxifen for postmenopausal women**: reduction of invasive BC only
  - Oxford: 1b A +*
- **AI for postmenopausal women**
  - Oxford: 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)
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**: +

- **Aromatase inhibitors**
  - **Oxford**
    - **LoE**: 1a
    - **GR**: A
    - **AGO**: +

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

* 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*  

Check list (inclusion criteria)  
Counseling for diagnostic genetic testing  
Communication, Exchange, Advice  
Genetic testing

Certified BC Center  
Prophylactic surgery  
Stratified therapy  
Familial BC Center  
Counseling: Indication for surveillance and/or prophylactic surgery

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

Breast Cancer Risk and Prevention