Breast Cancer Risk
and Prevention
Breast Cancer Risk and Prevention

- **Versions 2003–2019:**
  Schmutzler mit Albert / Bischoff / Blohmer / Ditsch / Fasching / Fehm / Kiechle / Maass / Müller-Schimpfle / Mundhenke / Rhiem / Rody / Schmidt / Schmutzler / Stickeler / Thomssen /

- **Version 2020:**
  Fasching / Rhiem
Principles of Prevention

- Women at increased risk for breast cancer are not considered patients but healthy women or counselees.

- A comprehensive informed consent taking into consideration all potential side effects and risks is warranted prior to offering preventive measures.

- Highest priority: „First, do no harm!“

(Primum nil nocere)
Who Should be Tested for BRCA1/2 Mutations and Possibly Further Risk Genes? (Part 1 of 2)

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. 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).
Who Should be Tested for *BRCA1/2* Mutations and Possibly Further Risk Genes? (Part 2 of 2)

Families with (each from one family branch)*

- 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
- 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 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)
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)

- Genetic risk factors:
  - BRCA1/2
  - Mod. penetrant risk genes
  - Other genes/genet. risk factors
- Non-genetic risk factors:
  - Reduced penetrance
  - Multifactorial

Disease risk vs. allele frequency (genetic variants): High risk alleles are very rare, while common alleles are associated with lower risk.
Breast Cancer Risk Genes with moderate to high Lifetime Risk

For following genes, risk calculations are available with varying degree of evidence. The clinical benefit must be proven by the effectiveness of preventive measures. ORs from studies with selected populations cannot be transferred to other populations.

Clinical benefit of genetic test

<table>
<thead>
<tr>
<th>Genes</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1(#), BRCA2*</td>
<td>1b</td>
<td>A</td>
<td>++°</td>
</tr>
<tr>
<td>PALB2(#), CDH1, TP53**</td>
<td>3a</td>
<td>B</td>
<td>+/-°</td>
</tr>
<tr>
<td>ATM, CHEK2, BARD1(#), RAD51C, RAD51D***</td>
<td>3a</td>
<td>B</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 ORs 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 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.
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, the 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></td>
<td>3a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>3b</td>
<td>D</td>
<td>--</td>
</tr>
<tr>
<td></td>
<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 centers of the GC-HBOC or cooperating centers
# 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)

**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>
</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 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.
- 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 case women already affected by primary breast cancer
- Allow appropriate time for consideration
# Multimodal Intensive Surveillance Program*

<table>
<thead>
<tr>
<th>Program für BRCA-Carriers</th>
<th>For the detection of early stage cancers</th>
<th>Oxford</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LoE 2b</td>
</tr>
<tr>
<td></td>
<td>Clinical breast exam</td>
<td>&gt; = 25 Jahre</td>
</tr>
<tr>
<td></td>
<td>Sonographie</td>
<td>&gt; = 25 Jahre</td>
</tr>
<tr>
<td></td>
<td>Mammogram</td>
<td>&gt; = 40 Jahre</td>
</tr>
<tr>
<td></td>
<td>Breast MRI</td>
<td>&gt; = 25 Jahre</td>
</tr>
</tbody>
</table>

For improvement of metastasis-free interval

- Survivors after tumors in childhood and radiotherapy of thoracic wall (e.g. M. Hodgkin)

<table>
<thead>
<tr>
<th>Oxford</th>
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<tbody>
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</table>

* The multimodal intensified early detection program should be carried out within the framework of transparent quality assurance and appropriate evaluation.
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).

High risk screening including MRI

Table 5  Detection performance of annual multimodality screening rounds with MRI by risk group, type of screening round and age

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>No. of rounds</th>
<th>No. of cancers</th>
<th>Detection rate %</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>PPV %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI</td>
<td>95% CI</td>
<td>95% CI</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>BRCA1 carriers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First rounds</td>
<td>2,750</td>
<td>83</td>
<td>25.5</td>
<td>20.2 to 32.0</td>
<td>84.3</td>
<td>75.0 to 90.6</td>
</tr>
<tr>
<td>Subsequent rounds</td>
<td>1,796</td>
<td>59</td>
<td>28.4</td>
<td>21.7 to 37.1</td>
<td>86.4</td>
<td>75.5 to 93.0</td>
</tr>
<tr>
<td>&lt; 30 years</td>
<td>247</td>
<td>3</td>
<td>8.1</td>
<td>2.2 to 29.0</td>
<td>66.7</td>
<td>20.8 to 93.9</td>
</tr>
<tr>
<td>30–39 years</td>
<td>579</td>
<td>28</td>
<td>43.2</td>
<td>29.4 to 63.0</td>
<td>89.3</td>
<td>72.8 to 96.3</td>
</tr>
<tr>
<td>40–49 years</td>
<td>642</td>
<td>17</td>
<td>21.8</td>
<td>13.0 to 36.3</td>
<td>82.4</td>
<td>59.0 to 93.8</td>
</tr>
<tr>
<td>≥ 50 years</td>
<td>328</td>
<td>11</td>
<td>30.5</td>
<td>16.6 to 55.2</td>
<td>90.9</td>
<td>62.3 to 98.4</td>
</tr>
<tr>
<td><strong>BRCA2 carriers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First rounds</td>
<td>1,724</td>
<td>53</td>
<td>27.8</td>
<td>21.1 to 36.7</td>
<td>90.6</td>
<td>79.7 to 95.9</td>
</tr>
<tr>
<td>Subsequent rounds</td>
<td>1,126</td>
<td>26</td>
<td>19.5</td>
<td>12.9 to 29.4</td>
<td>84.6</td>
<td>66.5 to 93.8</td>
</tr>
<tr>
<td>&lt; 30 years</td>
<td>119</td>
<td>0</td>
<td>0.0</td>
<td>0.0 to 31.3</td>
<td>89.1</td>
<td>82.2 to 93.5</td>
</tr>
<tr>
<td>30–39 years</td>
<td>309</td>
<td>9</td>
<td>22.7</td>
<td>11.0 to 46.0</td>
<td>77.8</td>
<td>45.3 to 93.7</td>
</tr>
<tr>
<td>40–49 years</td>
<td>452</td>
<td>12</td>
<td>24.3</td>
<td>13.6 to 43.0</td>
<td>91.7</td>
<td>64.6 to 98.5</td>
</tr>
<tr>
<td>≥ 50 years</td>
<td>246</td>
<td>5</td>
<td>16.3</td>
<td>6.3 to 41.1</td>
<td>80.0</td>
<td>37.6 to 96.4</td>
</tr>
<tr>
<td><strong>BRCA1/2 non-carriers with high risk</strong></td>
<td>9,668</td>
<td>85</td>
<td>8.3</td>
<td>6.7 to 10.3</td>
<td>94.1</td>
<td>87.0 to 97.5</td>
</tr>
</tbody>
</table>

CI confidence interval, PPV positive predictive value

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 > = 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)

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
</tbody>
</table>

* Follow-up care should be carried out as part of transparent quality assurance and appropriate evaluation.
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 an up to 1.8 to 3.75 times higher risk for prostatic cancer \(\leq 65\text{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\text{y}.

Currently, no specific surveillance is recommended

- For breast cancer:
  - self examination and watchful waiting
- For prostate cancer:
  - Compare recommendations on prostate carcinoma

*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

- 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>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2a</td>
<td>B</td>
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<tr>
<td></td>
<td>++*</td>
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<td></td>
<td>+++</td>
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<td></td>
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<tr>
<td></td>
<td>2a</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>++*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+*</td>
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</tbody>
</table>

* study participation recommended

** The RRSO is recommended from about 35 years for *BRCA1* and from about 40 years for *BRCA2* mutation carriers, taking into account the age of ovarian cancer diagnosis in the family and the family planning status.

*** No reduction in mortality could be shown for BRCA2 mutation carriers. RRM counselling should be individualised.
## Risk-reducing Interventions for BRCA1/2 Female Mutation Carriers Affected by Breast Cancer

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

* 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.

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.


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 *BRCA1/2*-associated Breast Cancer

Limited prospective cohort studies with short follow-up time

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

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

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

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

- PARP inhibitor in metastatic breast cancer  
  LoE 1b  
  Grade B  
  AGO +
Medical Prevention for Women at Increased Risk

- **Tamoxifen for women >35 years**: reduction of invasive BC, DCIS, and LN
  - Oxford LoE 1a, GR A, AGO +*

- **Raloxifen for postmenopausal women**: reduction of invasive BC only
  - Oxford LoE 1b, GR A, AGO +*

- **AI for postmenopausal women**:

  - Oxford LoE 1b, GR A, AGO +#

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# 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) 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*
- Aromatase inhibitors*
- Suppression of ovarian function* + Tamoxifen

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* Only proven for ER/PgR-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
Familial BC Center
Prophylactic surgery
Stratified therapy
Counseling: Indication for surveillance and/or prophylactic surgery

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