Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Breast Cancer Risk, Genetics and Prevention
Breast Cancer Risk and Prevention

- **Versions 2003–2021:**
  Albert / Bischoff / Blohmer / Ditsch / Fasching / Fehm / Kiechle / Maass / Müller-Schimpfle / Mundhenke / Park-Simon / Rhiem / Rody / Schmidt / Schmutzler / Stickeler / Thomssen / Witzel

- **Version 2022:**
  Dall / Ditsch / Gerber / 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)*
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
- two women with breast cancer, one < 50 yrs. (before the 51st birthday) or
- one woman affected by breast and one by ovarian cancer or
- one woman affected by breast and ovarian cancer or
- two women affected by ovarian cancer or
- one woman affected by bilateral breast cancer, first before the 51st birthday
- one woman affected by breast cancer < 35 yrs. (before the 36th birthday) or
- 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 \textit{BRCA1/2} Genes and Possibly Further Risk Genes?

(Part 2 of 2 - testing according to disease)

Oxford LoE: 2b \hspace{1cm} GR: B \hspace{1cm} AGO: ++

- Other recommended criteria:
  - own disease of triple negative breast cancer \(\leq 60\) yrs. of age
  - own disease of ovarian cancer
  - if therapeutically relevant (e.g. PARPi)
Checklist for Recording a Possible Hereditary Burden of Breast and / or Ovarian Cancer

https://checkliste.erbliche.belastung.brust.gyn-210212

online tool provided by the GC-HBOC,
https://familiaerer.brust-und-eierstockkrebs.uk-koeln.de/informationen/downloads/
State of Research: Relevance of Genetic and non-Genetic Risk Factors

- **Mod. penetrant risk genes**
- **Other genes/genet. risk factors**
- **Low risk variants/modifiers**

- **BRCA1/2**
- **Reduced penetrance**
- **Multifactorial**
- **Non-genetic**

The diagram illustrates the relative risk and allele frequency for various genes associated with breast cancer risk. Key genes include **BRCA1**, **BRCA2**, **CDH1**, **STK11**, **PALB2**, **PTEN**, **CHEK2**, **ATM**, and **Risk SNPs**.
Pathogenic Variants with Moderate to High Lifetime Risk for Breast Cancer

**Age-related risks for breast cancer**

- **high**: *BRCA1, BRCA2, PALB2*
- **high**: *CDH1, PTEN, TP53; STK11*#
- **moderate**: *ATM, CHEK2*
- **moderate**: *BARD1, RAD51C, RAD51D*

**Clinical benefit* of a genetic test**

<table>
<thead>
<tr>
<th>Genes</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>BRCA1, BRCA2</em></td>
<td>1b</td>
<td>A</td>
<td>++°</td>
</tr>
<tr>
<td><em>PALB2</em></td>
<td>3a</td>
<td>B</td>
<td>+°</td>
</tr>
<tr>
<td><em>CDH1, PTEN, TP53, STK11</em></td>
<td>3b</td>
<td>B</td>
<td>+°</td>
</tr>
<tr>
<td><em>ATM, BARD1, CHEK2, RAD51C, RAD51D</em></td>
<td>3a</td>
<td>B</td>
<td>+/- °</td>
</tr>
</tbody>
</table>

* Take into account the effectiveness of preventive measures and competing risks when making clinical decisions.

° Participation in prospective registries or studies is highly recommended.
### Breast Cancer Risk Category

<table>
<thead>
<tr>
<th>Lifetime risk from age 20</th>
<th>Near population risk of breast cancer</th>
<th>Moderate risk of breast cancer</th>
<th>High risk of breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 17%</td>
<td></td>
<td>Greater than 17% but less than 30%</td>
<td>30% or greater</td>
</tr>
<tr>
<td>Risk between ages 40 and 50</td>
<td>Less than 3%</td>
<td>3 to 8%</td>
<td>Greater than 8%</td>
</tr>
</tbody>
</table>

NICE (National Institute for Health and Care Excellence) guidance: Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer
Clinical guideline [CG164] Published: 25 June 2013 Last updated: 20 November 2019
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.

Conclusion:
The recommendations made here have been based on expert opinion using comprehensive literature ascertainment approach, but not systematic review. There is strong evidence that P/LP PALB2 variants confer a range of breast cancer risks across what is considered moderate to high; consequently, enhanced surveillance and the option of risk-reducing interventions are warranted.

The risk range for this gene underlies the need to move away from compartmentalizing PALB2 and consider risk to be a continuous variable from high to moderate, influenced by family history, polygenic risk score, and other factors. The same applies to other breast cancer genes. Changing this paradigm will allow us to move to personalized risk estimates by placing the risk from the P/LP variant in the context of other risk factors and develop strategies to translate this information to enhance medical management. There is reasonable evidence that PALB2 P/LP variants confer a small to moderately increased risk for ovarian cancer that may warrant risk-reducing interventions, albeit their clinical benefit is not sufficiently proven yet with respect to the efficacy of preventive measures to reduce morbidity and mortality. ...

Given the many uncertainties, those at risk for PALB2-related cancers, and the health professionals who care for them are encouraged to contribute follow-up data to long term studies, thereby facilitating the generation of prospective cancer risk estimates and the evaluation of prevention measures...

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.
- Individual low-risk variants increase the risk of disease only insignificantly. They have a multiplicative effect, so that the analysis of multiple gene regions (polygenic risk score, PRS) will be of clinical relevance in the future.

### Oxford

<table>
<thead>
<tr>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>2b</td>
<td>B</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 (polygenic risk score)
- Referral to centers of the GC-HBOC or cooperating centers

* Currently, moderately penetrant genes and low-risk variants should only be examined in the context of prospective cohort studies, such as that of the German consortium, in order to assess the clinical benefit.
## 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><em>TP53</em></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><em>PTEN</em></td>
<td>Breast, endometrium, thyroid, colorectal, kidney, melanoma</td>
</tr>
<tr>
<td>Hereditary diffuse gastric cancer syndrome</td>
<td><em>CDH1</em></td>
<td>Hereditary diffuse gastric cancer, lobular invasive breast cancer</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td><em>STK11/ LKB1</em></td>
<td>Colorectal, small intestine, stomach, pancreas, testicle, endometrium</td>
</tr>
<tr>
<td>Lynch</td>
<td><em>MLH1, MSH2, MSH6, PMS2, EPCAM</em></td>
<td>Endometrium, ovary, colorectal, small intestine, stomach, hepato biliary, pancreas, kidney, urogenital, CNS</td>
</tr>
<tr>
<td>Ataxia telangiectasia (AT-Syndrome)</td>
<td><em>ATM</em></td>
<td>Breast cancer, leukemia, stomach, melanoma, sarcoma</td>
</tr>
<tr>
<td>Franconi Anämie</td>
<td><em>BRCA2, BRIP1, RAD51C, PALB2</em></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)

<table>
<thead>
<tr>
<th>ATM</th>
<th>BARD1</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>BRIP1</th>
<th>CDH1</th>
<th>CHEK2</th>
<th>PALB2</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAD51C</td>
<td>RAD51D</td>
<td>TP53</td>
<td>EPCAM</td>
<td>MLH1</td>
<td>MSH2</td>
<td>MSH6</td>
<td>PMS2</td>
</tr>
<tr>
<td>PTEN</td>
<td>SMARCA4</td>
<td>STK11</td>
<td>APC</td>
<td>FAM175A</td>
<td>FANCC</td>
<td>FANCM</td>
<td>HOXB13</td>
</tr>
<tr>
<td>MEN1</td>
<td>MRE11A</td>
<td>MUTYH</td>
<td>NBN</td>
<td>NF1</td>
<td>POLD1</td>
<td>POLE</td>
<td>RAD50</td>
</tr>
<tr>
<td>RECQL</td>
<td>XRCC2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Selection of genes:**

- **11 BC (breast cancer) / OC (ovarian cancer) ‘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 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 validated 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
- The Medical Devices Act (e.g. risk assessment)
- Application of software for risk calculation requires professional training and experience

Communicate:
- Absolute cancer risks within a manageable timeframe
- Risk and benefit of a multimodal intensive surveillance program
- Risk and benefit of preventive clinical methods
- 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*

- Program for BRCA-mutation carriers without BC
- For the detection of early stage cancers
  - Clinical breast exam \( \geq 25 \) years Semi-annually
  - Sonographie \( \geq 25 \) years Semi-annually
  - Mammogram \( \geq 40 \) years Bi-annually
  - Breast MRI \( \geq 25 \) years Annually

- For improvement of metastasis-free interval

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

* The multimodal early detection program should be carried out for women with a pathogenic mutation in risk genes and those with an increased calculated risk without a mutation within the framework of transparent quality assurance and appropriate evaluation
# High-Risk Breast Cancer Surveillance with MRI

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

<table>
<thead>
<tr>
<th></th>
<th>30-39 years</th>
<th>40-49 years</th>
<th>≥ 50 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Detection rate (%)</td>
<td>PPV (%)</td>
<td>Detection rate (%)</td>
</tr>
<tr>
<td>BRCA1</td>
<td>43.2</td>
<td>29.4</td>
<td>21.8</td>
</tr>
<tr>
<td>BRCA2</td>
<td>22.7</td>
<td>23.3</td>
<td>24.3</td>
</tr>
<tr>
<td>BRCA1/2-non carriers with high risk</td>
<td>2.9</td>
<td>2.8</td>
<td>7.4</td>
</tr>
</tbody>
</table>

PPV: Positive predictive value

# Multimodal Surveillance Program for Female Carriers of Pathogenic BRCA Mutations after Primary Unilateral Breast Cancer

## Multimodal intensive surveillance program

### For detection of early stage breast cancers
- **Clinical breast exam** ≥ 25 years*
- **Sonographie** ≥ 25 years*
- **Mammogram** ≥ 40 years*
- **Breast MRI (until ACR1)** ≥ 25 years*

### 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>

* Aftercare should be carried out within the framework of transparent quality assurance and corresponding evaluation.

* or from age at initial diagnosis
Surveillance for Male Carriers of Pathogenic BRCA Mutations*

The lifetime risk of breast cancer in the general male population is 0.1 %. BRCA1 mutation carriers have a risk of breast cancer of about 1 % and an up to 1.8 to 3.75 times higher risk for prostatic cancer ≤ 65y.

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

Currently, no specific surveillance is recommended →
Early detection of cancer as part of standard care

- For breast cancer:
  self examination

- 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.
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.

<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>

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

<table>
<thead>
<tr>
<th>Procedure</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></td>
<td>2a</td>
<td>B</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>Risk-reducing bilateral mastectomy (RR-BM)</td>
<td></td>
<td>2b</td>
<td>B</td>
<td>+*</td>
</tr>
<tr>
<td>Reduces BC incidence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduces BC mortality in <em>BRCA1</em> mutation carriers***</td>
<td>2b</td>
<td>B</td>
<td></td>
<td>+*</td>
</tr>
</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>LoE</th>
<th>GRADE</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>
</tr>
<tr>
<td>- Reduces OvCa incidence and mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Reduces overall mortality (contradictory results for reduction of cl BC incidence)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylactic contralateral mastectomy (RR-CM)*</td>
<td>2b</td>
<td>B</td>
<td>+*</td>
</tr>
<tr>
<td>- Reduces BC incidence and mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen (reduces contralateral BC incidence)</td>
<td>2b</td>
<td>B</td>
<td>+/-*</td>
</tr>
<tr>
<td>Indication for RR-CM should consider age at onset of first breast cancer in affected gene</td>
<td>2a</td>
<td>B</td>
<td>+++*</td>
</tr>
<tr>
<td>RR-BM after ovarian cancer</td>
<td>4</td>
<td>C</td>
<td>+/-**</td>
</tr>
</tbody>
</table>

* Study participation recommended

** Depends on tumor stage (FIGO I/II), recurrence free interval (≥ 5 yrs.), 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)
- Systemic therapy according to sporadic breast cancer
- gBRCA mutation status is predictive for chemotherapy response in TNBC
- Carboplatin (vs. Docetaxel) in metastatic breast cancer

PARP inhibitor (Her2-negative carcinomas):

- EBC: Olaparib (in case of gBRCA1/2 mutation)*
- MBC:
  - gBRCA1/2 mutation
    - Olaparib
    - Talazoparib
  - Somatic BRCA1/2 mutation (germline testing is standard)
    - Olaparib
  - gPALB2
    - Olaparib

EBC: Early Breast Cancer; MBC: Metastatic Breast Cancer; * Use according to study inclusion criteria and approval
**Medical Prevention for Women at Increased Risk**

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen for women &gt; 35 years: reduction of invasive BC, DCIS and LN</td>
<td>1a</td>
<td>A</td>
<td>+*</td>
</tr>
<tr>
<td>Raloxifen for postmenopausal women: reduction of invasive BC only</td>
<td>1b</td>
<td>A</td>
<td>+*</td>
</tr>
<tr>
<td>AI for postmenopausal women</td>
<td>1b</td>
<td>A</td>
<td>+**</td>
</tr>
</tbody>
</table>

* Risk situation as defined in NSABP P1-trial (1.66 % in 5 years) or according to #Tyrer-Cuzick model (IBIS-II)

** 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.
Cooperation of Certified Breast Cancer (BC) Centres (Ctr) with Certified 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