Diagnostic and Treatment of Patients with Primary and Metastatic Breast Cancer

Breast Cancer Risk and Prevention
Breast Cancer Risk and Prevention

- **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)


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/qualitaets sicherung/Zertifizierungsstelle/KB-erbliche_Belastung_V2016-01-06.pdf


# 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.

<table>
<thead>
<tr>
<th>Clinical benefit of genetic test</th>
<th>Oxford 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>
</tr>
<tr>
<td><strong>PALB2, CDH1, TP53</strong></td>
<td>3a</td>
<td>C</td>
<td>+/-*</td>
</tr>
<tr>
<td><strong>ATM, CHEK2, BARD1, BRIP1, MSH6, RAD51D</strong></td>
<td>3a</td>
<td>C</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 penetances are not yet available.

** This cases are classified as genes with a moderate lifetime risk based on the currently available data.

* Participation in prospective registries or studies is highly recommended.


### 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, PMSZ, 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, leukaemia, stomach, melanoma, sarcoma</td>
</tr>
<tr>
<td>Franconi Anämie</td>
<td>BRCA2, BRIP1, RAD51C, PALB2</td>
<td>AML, MDS, SCC, medullloblastoma, nephroblastoma, breast, pancreas, ovary</td>
</tr>
<tr>
<td>Nijmegen-Breakage Syndrome</td>
<td>NBN</td>
<td>Leukemia, lymphoma</td>
</tr>
</tbody>
</table>


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

<table>
<thead>
<tr>
<th>Gene</th>
<th>AT1</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>BRI1</th>
<th>CDH1</th>
<th>CHEK2</th>
<th>PALB2</th>
<th>RAD51C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<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


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</td>
<td>0.001 – 0.049</td>
</tr>
<tr>
<td></td>
<td>significance</td>
<td></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.

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

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

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


2. Aktualisierte Empfehlungen nach Bewertung von Gdablagerungen im Gehirn und anderen Geweben (08.01.2018) durch EMA und BfArM


### 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

<table>
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<tbody>
<tr>
<td>2a</td>
<td>B</td>
<td>+*</td>
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</table>

- Unilateral or bilateral mastectomy is not indicated in the absence of clearly defined genetic risk factors

* study participation recommended

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

RR-BSO is recommended after completion of family planning
RR-BM revealed a high incidence of premalignant lesions

Oxford LoE GR AGO
2c B ++*
2c B +*

* study participation recommended


Therapy of BRCA1/2-associated Breast Cancer

Limited prospective cohort studies with short follow-up time

1. Breast converting surgery: adequate local tumor control (~10 years observation)
2. Systemic therapy according to sporadic breast cancer
3. gBRCA1 mutation status is predictive for chemotherapy response in TNBC
4. Carboplatin (vs. Docetaxel) in metastatic breast cancer
5. PARP inhibitor in metastatic breast cancer + prognosis must be taken into account

Oxford LoE GR AGO

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<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>3a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
<td>+</td>
</tr>
</tbody>
</table>


SABCS:
Robson - OlympiaD
Litton SABCS - EMBRACA
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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<tbody>
<tr>
<td>1a</td>
<td>A</td>
<td></td>
<td>+*</td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
<td></td>
<td>+*</td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
<td></td>
<td>+*</td>
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</table>

* 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 Lpsi- and Contralateral Breast Cancer

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

<table>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen*</td>
<td>1a A</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Aromatasehemmer*</td>
<td>1a A</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Suppression of ovarian function* + Tamoxifen</td>
<td>1b B</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

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


