

Diagnostic and Treatment of Patients with Primary and Metastatic Breast Cancer



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Version 2018.1

Breast Cancer Risk and Prevention

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

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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?

Oxford LoE: 2b GR: B AGO: ++

- 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 $\geq 10\%$ 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 $\geq 10\%$ 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)*

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8350379533 Checklist zur Erfassung einer möglichen erblichen Belastung für Brust-und/oder Eierstockkrebs (Mamma-Ca incl. DCIS)

Name der Patientin: _____ Geburtsdatum: _____

A. Patientin oder Patient und deren Eltern/Geschwister/Kinder	ggf. Anzahl (Nur ankreuzen)	Gewichtung	Ergebnis
Auftreten			
eines Mamma-Karzinoms bei der Patientin vor dem 36. LJ	<input type="checkbox"/> 1	3	<input type="checkbox"/>
eines unilateralen Mamma-Karzinoms bei der Patientin vor dem 51. LJ	<input type="checkbox"/> 1	2	<input type="checkbox"/>
eines bilateralen Mamma-Karzinoms bei der Patientin, das erste vor dem 51. LJ	<input type="checkbox"/> 1	3	<input type="checkbox"/>
eines uni- oder bilateralen Mamma-Karzinoms bei der Patientin nach dem 50. LJ	<input type="checkbox"/> 1	1	<input type="checkbox"/>
eines Ovarial-/Tuberkarzinoms oder einer primären Peritonealkarzinose bei der Patientin	<input type="checkbox"/> 1	2	<input type="checkbox"/>
eines uni- oder bilateralen Mammakarzinoms bei einem Patienten (mml.)	<input type="checkbox"/> 1	2	<input type="checkbox"/>
eines Mamma-Karzinoms bei Schwestern/Töchtern/Mutter/Nichten vor dem 36. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	3	<input type="checkbox"/>
eines unilateralen Mamma-Karzinoms bei Schwestern/Töchtern/Mutter/Nichten vor dem 51. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
eines bilat. Mamma-Karzinoms bei Schwestern/Töchtern/Mutter/Nichten, das erste vor dem 51. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	3	<input type="checkbox"/>
eines uni- oder bilat. Mamma-Karzinoms bei Schwestern/Töchtern/Mutter/Nichten nach dem 50. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	1	<input type="checkbox"/>
eines Mamma-Karzinoms bei Brüdern/Söhnen/Vater/Neffen	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
eines Ovarial-/Tuberkarzinoms/primären Peritonealkarzinose bei Schwestern/Töchtern/Mutter/Nichten	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
Summe Patientin und deren Eltern/Geschwister/Kinder			A <input type="text"/>
B. Weitere mütterliche Linie	Anzahl (Nur ankreuzen)	Gewichtung	Ergebnis
Auftreten			
eines Mamma-Karzinoms bei einer Angehörigen vor dem 36. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	3	<input type="checkbox"/>
eines unilateralen Mamma-Karzinoms bei einer Angehörigen vor dem 51. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
eines bilateralen Mamma-Karzinoms bei einer Angehörigen, das erste vor dem 51. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	3	<input type="checkbox"/>
eines uni- oder bilateralen Mamma-Karzinoms bei einer Angehörigen nach dem 50. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	1	<input type="checkbox"/>
eines Mamma-Karzinoms bei einem angehörigen Mann	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
eines Ovarial-/Tuberkarzinoms oder einer primären Peritonealkarzinose bei einer Angehörigen	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
Summe weitere mütterliche Linie			B <input type="text"/>
C. weitere väterliche Linie	Anzahl (Nur ankreuzen)	Gewichtung	Ergebnis
Auftreten			
eines Mamma-Karzinoms bei einer Angehörigen vor dem 36. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	3	<input type="checkbox"/>
eines unilateralen Mamma-Karzinoms bei einer Angehörigen vor dem 51. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
eines bilateralen Mamma-Karzinoms bei einer Angehörigen, das erste vor dem 51. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	3	<input type="checkbox"/>
eines uni- oder bilateralen Mamma-Karzinoms bei einer Angehörigen nach dem 50. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	1	<input type="checkbox"/>
eines Mamma-Karzinoms bei einem angehörigen Mann	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
eines Ovarial-/Tuberkarzinoms oder einer primären Peritonealkarzinose bei einer Angehörigen	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
Summe weitere väterliche Linie			C <input type="text"/>
D. Der höhere Wert aus B und C			D <input type="text"/>
E. Summe aus A und D = Risiko-Score	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> >7		A+D <input type="text"/>

Version: 06. Januar 2016 © Ärztekammer Westfalen-Lippe, Deutsche Krebsgesellschaft, Deutsche Gesellschaft für Gynäkologie, Deutscher Konsortium für Erblicher Brust- und Eierstockkrebs

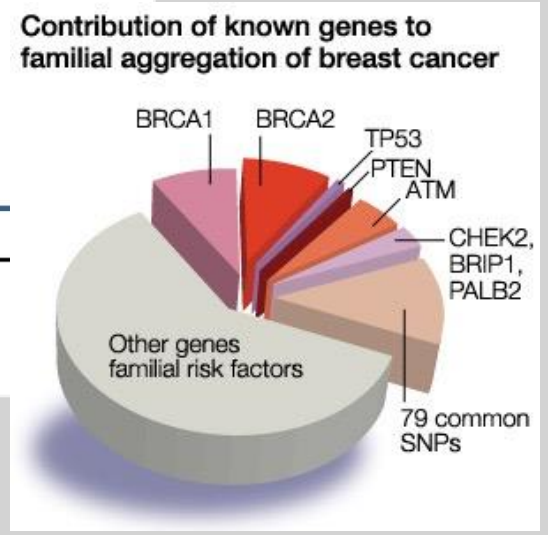
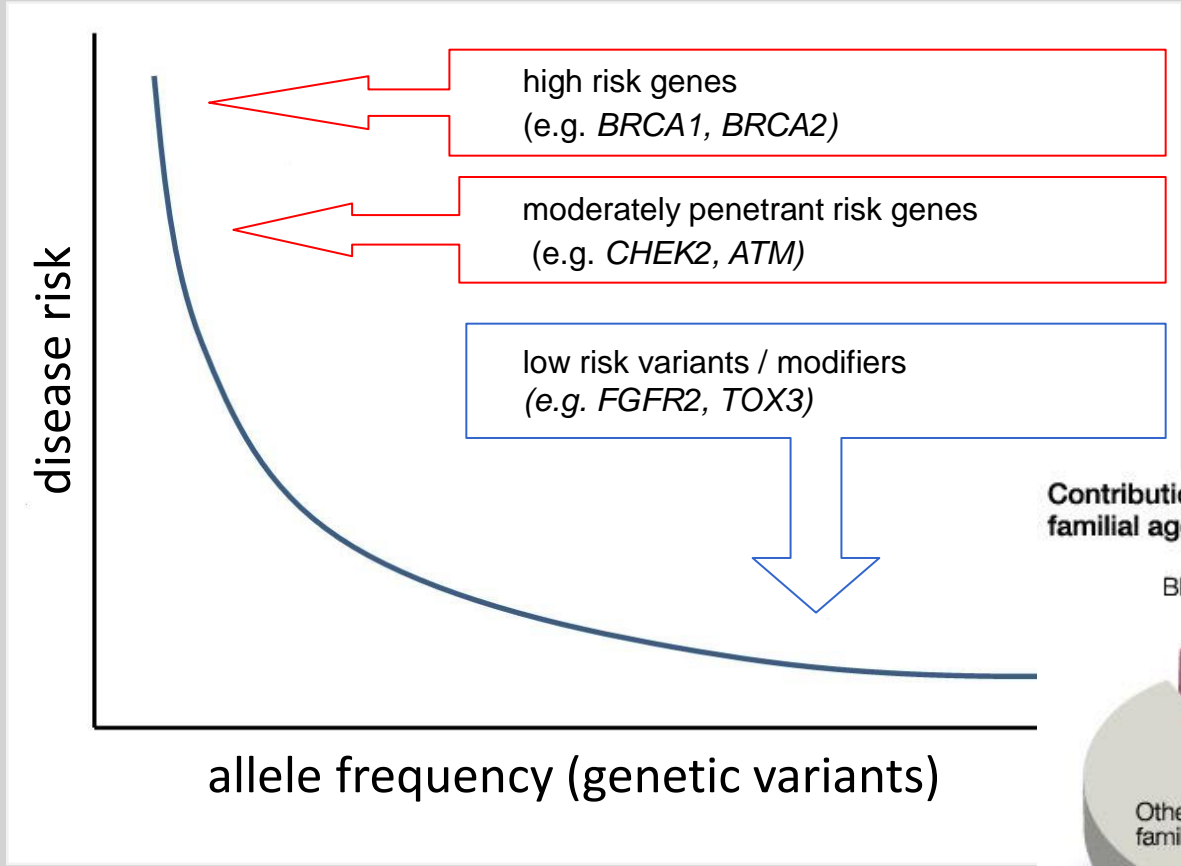
www.ago-online.de

* 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

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Breast Cancer Risk Genes with moderate to high Lifetime Risk

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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

- *BRCA1, BRCA2**
- *PALB2, CDH1, TP53***
- *ATM, CHEK2, BARD1, BRIP1, MSH6, RAD51D****

	Oxford		
	LoE	GR	AGO
	2a/1b	A	++ [°]
	3a	C	+/- [°]
	3a	C	+/- [°]

* *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.

▪ *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

	Oxford		
	LoE	GR	AGO
	3a	B	+/-
	3b	D	--
	5	D	+

Non BRCA-associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer

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

Breast Cancer Gene Panels (e.g.)

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BROCA gene panel (cross-cancer, <http://web.labmed.washington.edu/tests/genetics/BROCA>)

AKT1
APC
ATM
ATR
AXIN2
BAP1
BARD1
BMPR1A
BRCA1
BRCA2
BRIP1
CDH1
CDK4
CDKN2A
CHEK1
CHEK2
CTNNA1
EPCAM
FAM175A
FANCM
FH
GALNT12
GEN1
GREM1
HOXB13
MEN1
MET
MITF
MLH1
MRE11A
MSH2+EPCAM
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

AMBRY Genetics BreastNext <http://www.ambrygen.com/tests/breastnext>

ATM
BARD1
BRCA1
BRCA2
BRIP1
CDH1
CHEK2
MRE11A
MUTYH
NBN
NF1
PALB2
PTEN
RAD50
RAD51C
RAD51D
TP53

CEGAT CAN02: Brust- und Ovarialkarzom http://www.cegat.de/Tumorerkrankungen_171.html

ATM
BARD1
BRCA1
BRCA2
BRIP1
CDH1
CHEK2
EPCAM
FAM175A
FANCA
FANCC
FANCD2
FANCE
FANCF
FANCG
HOXB13
MEN1
MLH1
MRE11A
MSH2
MSH3
MSH6
MUTYH
NBN
NF1
PALB2
PMS2
PTCH1
PTEN
RAD50
RAD51C
RAD51D
RAD51D
RINT1
SDHB
SDHC
SDHD
SLX4
STK11
TP53
XRCC2

TruSight™ Cancer (illumina) http://res.illumina.com/documents/products/5Cdatasheets/5Cdatasheet_truSight_cancer.pdf

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
ERCC2
ERCC3
ERCC4
ERCC5
EXT1
EXT2
EZH2
FANCA
FANCB
FANCC
FANCD2
FANCE
FANCF
FANCG
FANCI
FANCL
FANCM
FH
FLCN
GATA2
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
RB1
RECQL4
RET
RHBDF2
RUNX1
SBDS
SDHAF2
SDHB
SDHC
SDHD
SLX4
SMAD4
SMARCB1
STK11
SUFU
TMEM127
TP53
TSC1
TSC2
VHL
WRN
WT1
XPA
XPC

CENTOGENE Breast <https://www.centogene.com/centogene>

ATM
BARD1
BRCA1
BRCA2
BRIP1
CDH1
CHEK2
NBN
PALB2
PTEN
RAD51C
STK11
TP53

MYRIAD myRISK Panel

APC
ATM
BARD1
BMPR1A
BRCA1
BRCA2
BRIP1
CDH1
CDK4
CDKN2A
CHEK2
EPCAM
GREM1
MLH1
MSH2
MSH6
MUTYH
NBN
PALB2
PMS2
POLD1
POLE
PTEN
RAD51C
RAD51D
SMAD4
STK11
TP53

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

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<i>ATM</i>	<i>BRCA1</i>	<i>BRCA2</i>	<i>BRIP1</i>	<i>CDH1</i>	<i>CHEK2</i>	<i>PALB2</i>	<i>RAD51C</i>
<i>RAD51D</i>	<i>TP53</i>	<i>EPCAM</i>	<i>MLH1</i>	<i>MSH2</i>	<i>MSH6</i>	<i>PMS2</i>	<i>BARD1</i>

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

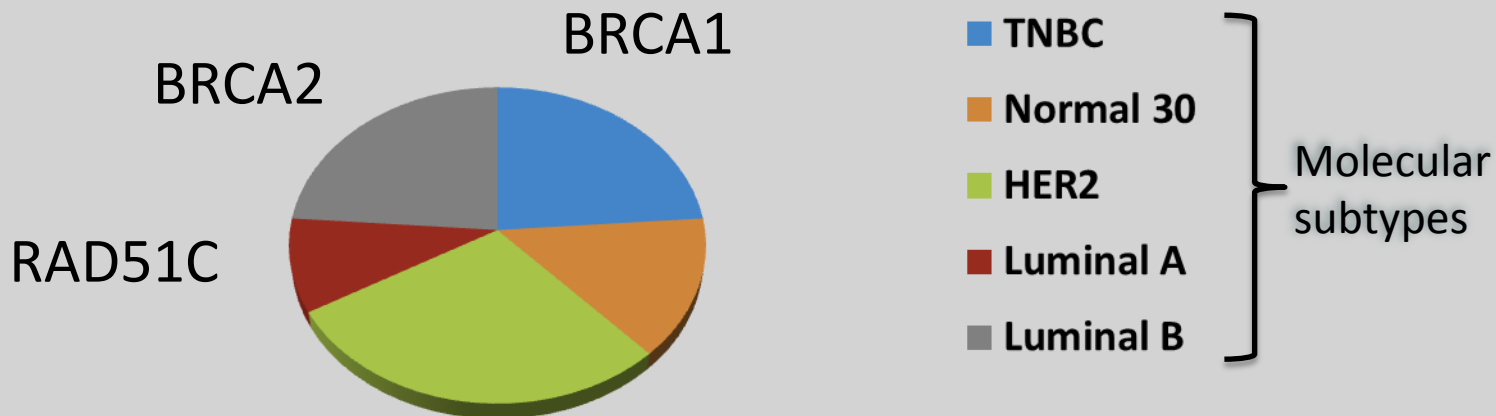
Strategy:

- Validation in large cohort, constant expansion and improvement

Clinical Implication: Genotype/Phenotype

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**Genotype determines not only disease penetrance but
phenotype and clinical disease course**

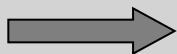
Distinct Genetically Subtypes Defines Distinct Tumor Entities

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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

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- **„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)



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Proposed Classification System for Sequence Variants Identified by Genetic Testing

Class	Description	Probability of being pathogenic
5	Definitely pathogenic	> 0,99
4	Likely pathogenic	0,95 – 0,99
3	Uncertain	0,05 – 0,949
2	Likely not pathogenic or of little clinical significance	0,001 – 0,049
1	Not pathogenic or no of clinical significance	< 0,001

Only class 4 and 5 variants are considered clinically relevant.

Classification of IARC Class 3 Variants

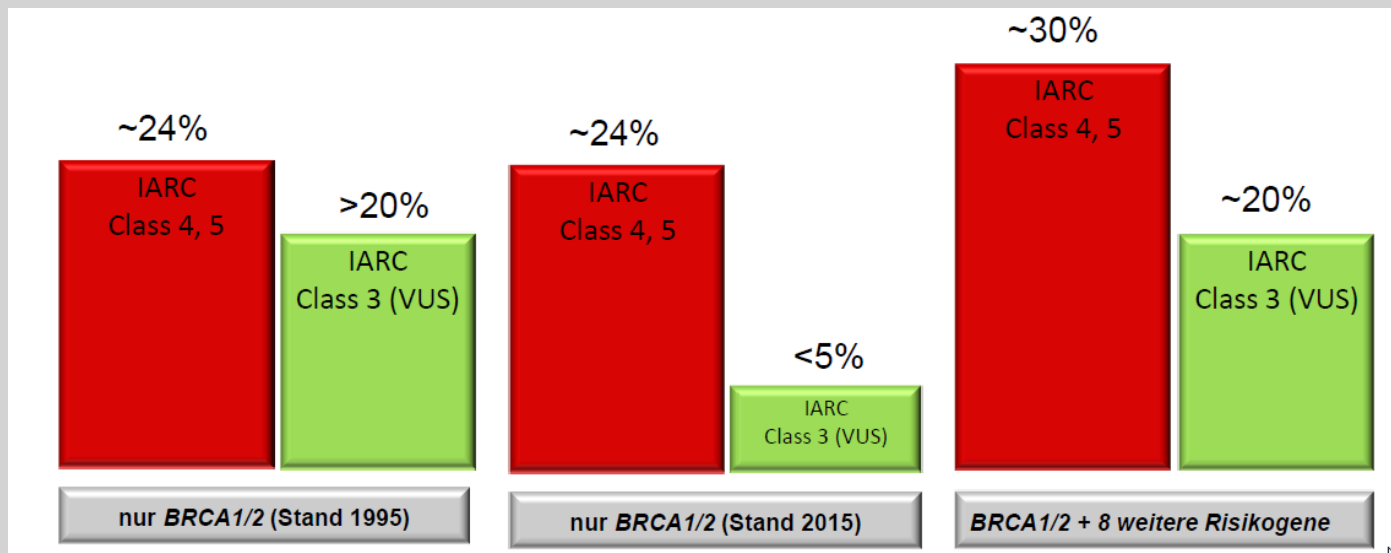
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Requires additional information and analyses, e.g.

- Co-occurrence data from large data banks
- Segregation analysis
- Functional analysis etc.

To be accumulated by large study groups such as ENIGMA



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

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Oxford		
LoE	GR	AGO
5	D	++

- 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*

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		Oxford		
		LoE	GR	AGO
■ Program für BRCA-Carriers				
■ For the detection of early stage cancers		2b	B	++
■ Clinical breast exam	>= 25 Jahre	Semi-annually		
■ Sonographie (Intervall between MRI)	>= 25 Jahre	Annually		
■ Mammogram	>= 40 Jahre	Biannual		
■ Breast MRI	>= 25 Jahre	annual		
■ For reduction of metastasis free interval		2b	B	+
■ Survivors after tumors in chuldhood and radiotherapy of thoracic wall (e.g. M. Hodgkin)		2a	B	++

* 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 *



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			Oxford		
			LoE	GR	AGO
■ Multimodal intensive surveillance program lifelong					
■ For the detection of early stage breast cancers			2a	B	++
■ Clinical breast exam	>= 25 Jahre		Semi-annually		
■ Sonographie	>= 25 Jahre		Semi-annually		
■ Mammogram	>= 40 Jahre		Biannual		
■ Breast MRI (until ACR1)	>= 25 Jahre		annual		
■ For mortality reduction (10 year survival)			4	C	+/-*

- 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)

* 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 \leq 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 \leq 65y.

Currently no specific surveillance is recommended

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

Oxford		
LoE	GR	AGO
5	D	+
3b	C	+

* 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

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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

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

Oxford		
LoE	GR	AGO
2a	B	+*

* study participation recommended

Surgical Prevention for Healthy Female *BRCA1/2* Mutation Carriers

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

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

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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Risk-reducing bilateral salpingo-oophorectomy (RR-PBSO, PBSO) <ul style="list-style-type: none"> Reduces OvCa incidence and mortality Reduces BrCa incidence and mortality Reduces overall mortality (contradictory results for reduction of cl BrCa incidence) 	2b	B	+*
<ul style="list-style-type: none"> Prophylactic contralateral mastectomy (RR-BM, PBM) <ul style="list-style-type: none"> Reduces BrCa incidence and mortality 	2b	B	+*
<ul style="list-style-type: none"> Tamoxifen (reduces cl BrCa incidence) 	2b	B	+/-*
<ul style="list-style-type: none"> Indication for PBM should consider age at onset of first breast cancer in affected gene 	2a	B	++*
<ul style="list-style-type: none"> Prophylactic bilateral mastectomy after ovarian cancer 	4	C	+/-**

* 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

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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.

Int J Cancer. 2015 Feb 1;136(3):668-77. doi: 10.1002/ijc.29032. Epub 2014 Jul 8.

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 *BRCA1/2*-associated Breast Cancer

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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**
- **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**

Oxford		
LoE	GR	AGO

2a	B	+
----	---	---

3a	B	+
----	---	---

2b	B	+
----	---	---

2b	B	+
----	---	---

1b	A	+
----	---	---

Medical Prevention for Women at Increased Risk

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- **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**

	Oxford		
	LoE	GR	AGO
	1a	A	+*
	1b	A	+*
	1b	A	+[#]

* 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

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

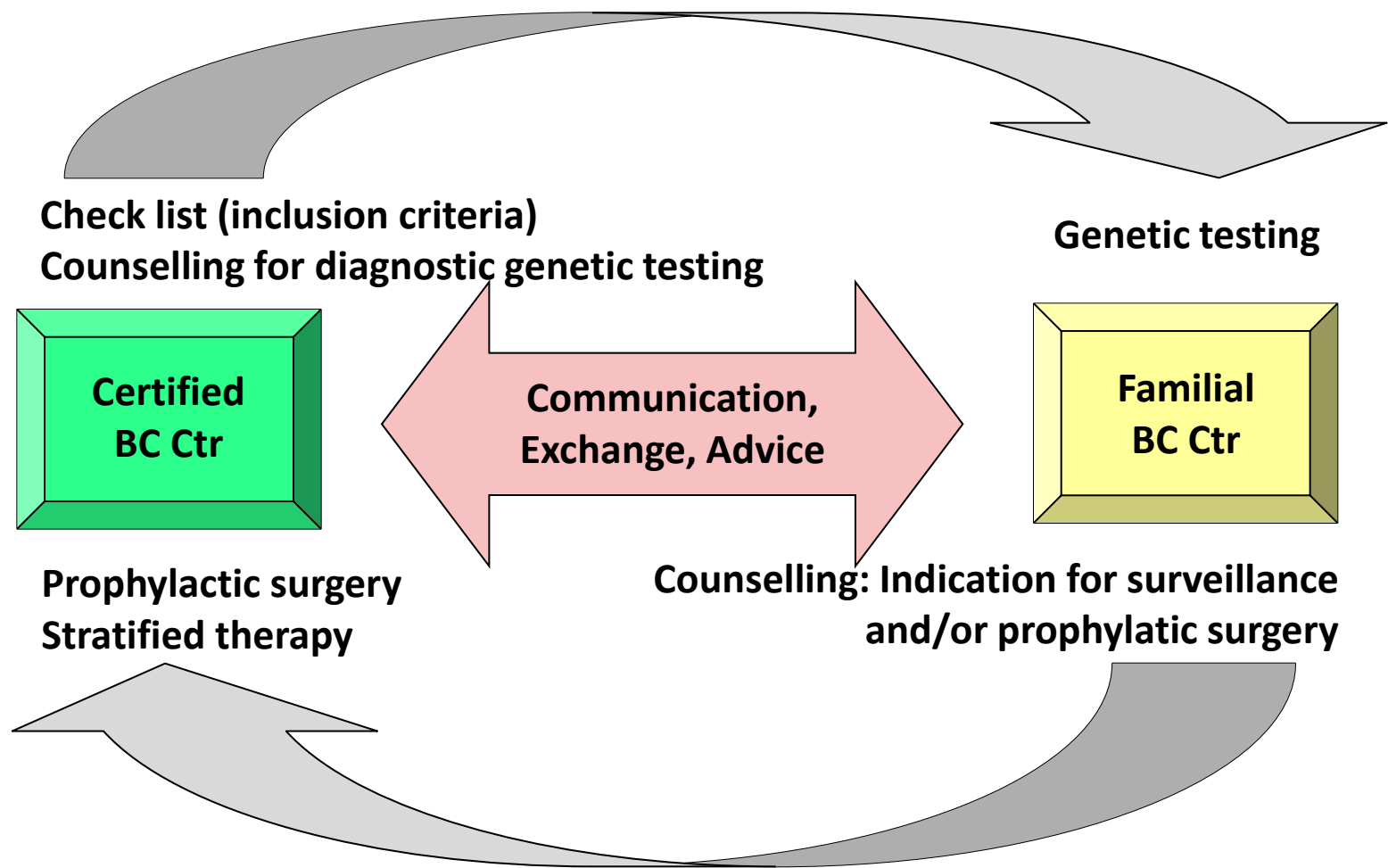
- **Tamoxifen***
- **Aromatasehemmer***
- **Suppression of ovarian function* + Tamoxifen**

Oxford		
LoE	GR	AGO
1a	A	+
1a	A	+
1b	B	+

Cooperation of Certified Breast Cancer (BC) Centres (Ctr) with Familial BC Ctr of the GC-HBOC*

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