Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2020.1

Breast Cancer Risk and Prevention

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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

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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? (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).

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

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

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#)*

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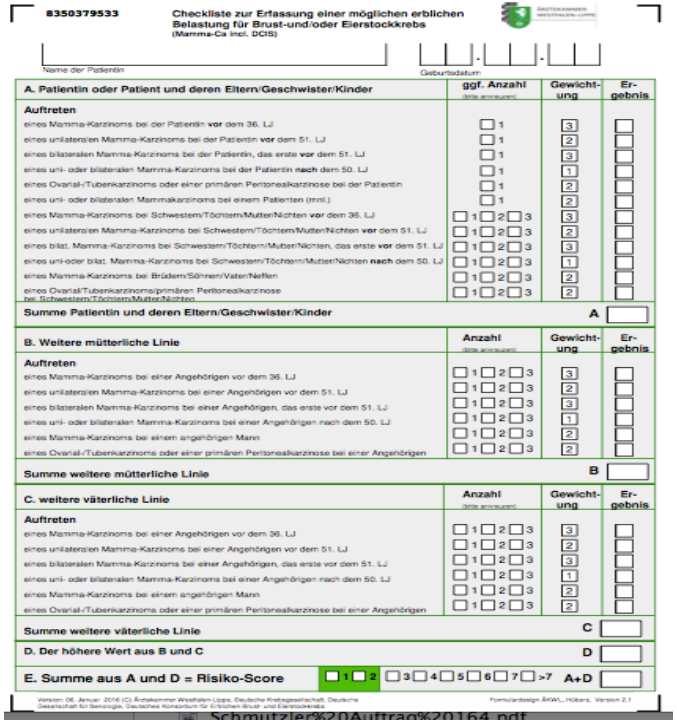

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Checkliste zur Erfassung einer möglichen erblichen Belastung für Brust-und/oder Eierstockkrebs
(Mamma-Ca incl. DCIS)

Name der Patientin | Geburtsdatum

A. Patientin oder Patient und deren Eltern/Geschwister/Kinder	ggf. Anzahl	Gewichtung	Ergebnis
Auftreten			
eines Mamma-Karzinoms bei der Patientin **vor** dem 36. LJ	☐1	3	☐
eines unilateralen Mamma-Karzinoms bei der Patientin **vor** dem 51. LJ	☐1	2	☐
eines bilateralen Mamma-Karzinoms bei der Patientin, das erste **vor** dem 51. LJ	☐1	3	☐
eines uni- oder bilateralen Mamma-Karzinoms bei der Patientin **nach** dem 50. LJ	☐1	1	☐
eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei der Patientin	☐1	2	☐
eines uni- oder bilateralen Mammakarzinoms bei einem Patienten (mnl.)	☐1	2	☐
eines Mamma-Karzinoms bei Schwestern/Töchtern/Mutter/Nichten **vor** dem 36. LJ	☐1☐2☐3	3	☐
eines unilateralen Mamma-Karzinoms bei Schwestern/Töchtern/Mutter/Nichten **vor** dem 51. LJ	☐1☐2☐3	2	☐
eines bilat. Mamma-Karzinoms bei Schwestern/Töchtern/Mutter/Nichten, das erste **vor** dem 51. LJ	☐1☐2☐3	3	☐
eines uni-oder bilat. Mamma-Karzinoms bei Schwestern/Töchtern/Mutter/Nichten **nach** dem 50. LJ	☐1☐2☐3	1	☐
eines Mamma-Karzinoms bei Brüdern/Söhnen/Vater/Neffen	☐1☐2☐3	2	☐
eines Ovarial/Tubenkarzinoms/primären Peritonealkarzinose bei Schwestern/Töchtern/Mutter/Nichten	☐1☐2☐3	2	☐
Summe Patientin und deren Eltern/Geschwister/Kinder			A ☐

B. Weitere mütterliche Linie	Anzahl	Gewichtung	Ergebnis
Auftreten			
eines Mamma-Karzinoms bei einer Angehörigen vor dem 36. LJ	☐1☐2☐3	3	☐
eines unilateralen Mamma-Karzinoms bei einer Angehörigen vor dem 51. LJ	☐1☐2☐3	2	☐
eines bilateralen Mamma-Karzinoms bei einer Angehörigen, das erste vor dem 51. LJ	☐1☐2☐3	3	☐
eines uni- oder bilateralen Mamma-Karzinoms bei einer Angehörigen nach dem 50. LJ	☐1☐2☐3	1	☐
eines Mamma-Karzinoms bei einem angehörigen Mann	☐1☐2☐3	2	☐
eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei einer Angehörigen	☐1☐2☐3	2	☐
Summe weitere mütterliche Linie			B ☐

C. weitere väterliche Linie	Anzahl	Gewichtung	Ergebnis
Auftreten			
eines Mamma-Karzinoms bei einer Angehörigen vor dem 36. LJ	☐1☐2☐3	3	☐
eines unilateralen Mamma-Karzinoms bei einer Angehörigen vor dem 51. LJ	☐1☐2☐3	2	☐
eines bilateralen Mamma-Karzinoms bei einer Angehörigen, das erste vor dem 51. LJ	☐1☐2☐3	3	☐
eines uni- oder bilateralen Mamma-Karzinoms bei einer Angehörigen nach dem 50. LJ	☐1☐2☐3	1	☐
eines Mamma-Karzinoms bei einem angehörigen Mann	☐1☐2☐3	2	☐
eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei einer Angehörigen	☐1☐2☐3	2	☐
Summe weitere väterliche Linie			C ☐
D. Der höhere Wert aus B und C			D ☐
E. Summe aus A und D = Risiko-Score	☐1☐2☐3☐4☐5☐6☐7☐>7		A+D ☐

Version: 06. Januar 2016 (C) Ärztekammer Westfalen-Lippe, Deutsche Krebsgesellschaft, Deutsche Gesellschaft für Senologie, Deutsches Konsortium für Erblichen Brust- und Eierstockkrebs — Formulardesign: ÄKWL, Hübers, Version 2.1

Schmutzler%20Auftrag%20164.pdf

* **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)**
https://www.aekwl.de/fileadmin/qualitaetssicherung/Zertifizierungsstelle/2018-07-17-CL-Genetik.pdfc

State of research: Relevance of genetic and non-genetic risk factors

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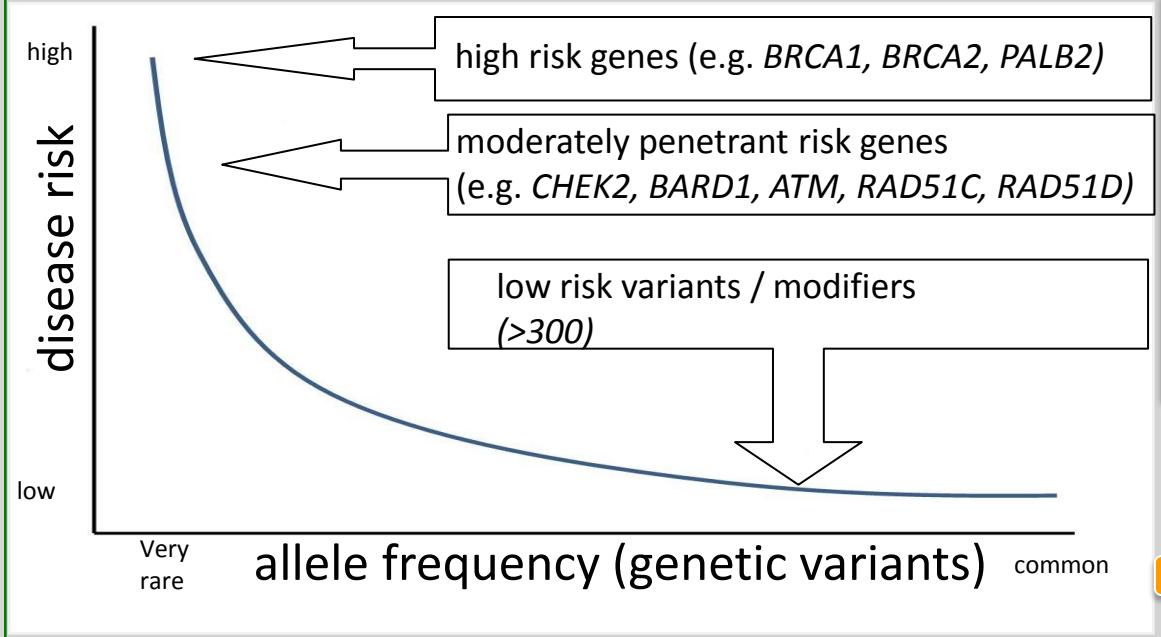

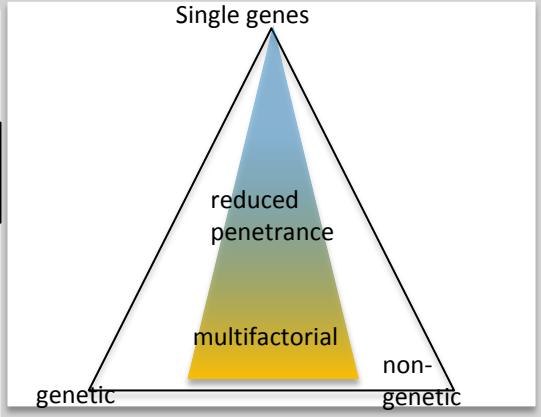

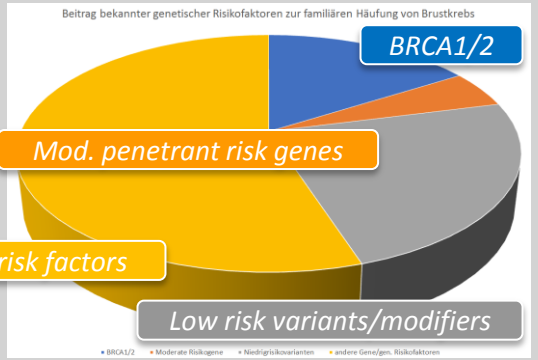

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Breast Cancer Risk Genes with moderate to high Lifetime Risk

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	Oxford LoE	Oxford GR	AGO
▪ *BRCA1(#), BRCA2**	1b	A	++°
▪ *PALB2(#) , CDH1, TP53***	3a	B	+/-°
▪ *ATM, CHEK2, BARD1(#) , RAD51C, RAD51D****	3a	B	+/-°

* *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.

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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).**

	Oxford		
	LoE	GR	AGO
Clinical genetic testing of moderate-risk genes, e.g. gene panels	3a	B	+/-
Clinical genetic testing for low-risk variants	3b	D	--
Referral to centers of the GC-HBOC or cooperating centers	5	D	+

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

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

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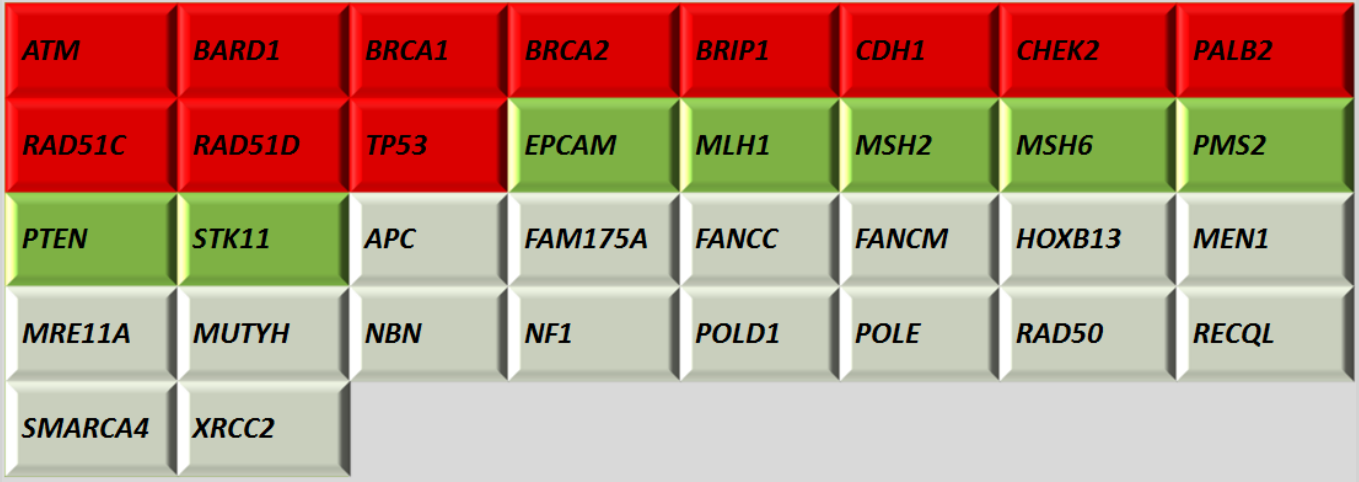
Current version of the TruRisk® BC/OC* Gene Panel by the German Consortium (GC-HBOC)



Selection of genes:

11 BC/OC 'core genes' (Data on risk increase)

7 other s**yndrome-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

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FORSCHEN
LEHREN
HEILEN

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 adressed:

- 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 <u>extremely rare</u> (≤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-occurence 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

Class	Discription	Probabilty of being pathogenic
5	Definitly 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

Requires additional information and analyses, e.g.

- **Co-occurence 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 critiera 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 valide 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, e.g.** "Präventive Gendiagnostik - Hoffnung und Fluch der Genanalyse", Heft 26 des Deutschen Ärzteblattes vom 29.06.2012; Dtsch. Ärztebl. 2012; 109(26): A-1371 / B-1183 / C-1163)

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

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Multimodal Intensive Surveillance Program*

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

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

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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).**

Bick U, Engel C, Krug B, et al. High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer. *Breast Cancer Res Treat*. 2019;175(1):217–228. doi:10.1007/s10549-019-05152-9

High risk screening including MRI

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

	No. of rounds	No. of cancers	Detection rate		Sensitivity		Specificity		PPV	
			‰	95% CI	%	95% CI	%	95% CI	%	95% CI
BRCA1 carriers	2,750	83	25.5	20.2 to 32.0	84.3	75.0 to 90.6	90.1	88.9 to 91.2	21.0	17.0 to 25.7
First rounds	954	24	19.9	12.8 to 30.9	79.2	59.5 to 90.8	86.2	83.9 to 88.3	12.9	8.4 to 19.3
Subsequent rounds	1,796	59	28.4	21.7 to 37.1	86.4	75.5 to 93.0	92.2	90.9 to 93.4	27.4	21.5 to 34.2
< 30 years	247	3	8.1	2.2 to 29.0	66.7	20.8 to 93.9	94.3	90.6 to 96.6	12.5	3.5 to 36.0
30–39 years	579	28	43.2	29.4 to 63.0	89.3	72.8 to 96.3	89.1	86.2 to 91.4	29.4	20.8 to 39.8
40–49 years	642	17	21.8	13.0 to 36.3	82.4	59.0 to 93.8	93.4	91.2 to 95.1	25.5	15.8 to 38.3
≥ 50 years	328	11	30.5	16.6 to 55.2	90.9	62.3 to 98.4	93.7	90.5 to 95.9	33.3	19.2 to 51.2
BRCA2 carriers	1,724	53	27.8	21.1 to 36.7	90.6	79.7 to 95.9	90.2	88.7 to 91.6	22.7	17.6 to 28.9
First rounds	598	27	43.5	29.8 to 62.9	96.3	81.7 to 99.3	85.1	82.0 to 87.8	23.4	16.5 to 32.1
Subsequent rounds	1,126	26	19.5	12.9 to 29.4	84.6	66.5 to 93.8	92.9	91.2 to 94.3	22.0	15.0 to 31.1
< 30 years	119	0	0.0	0.0 to 31.3			89.1	82.2 to 93.5	0	0.0 to 22.8
30–39 years	309	9	22.7	11.0 to 46.0	77.8	45.3 to 93.7	92.3	88.8 to 94.8	23.3	11.8 to 40.9
40–49 years	452	12	24.3	13.6 to 43.0	91.7	64.6 to 98.5	93.4	90.7 to 95.4	27.5	16.1 to 42.8
≥ 50 years	246	5	16.3	6.3 to 41.1	80.0	37.6 to 96.4	94.6	91.0 to 96.8	23.5	9.6 to 47.3
BRCA1/2 non-carriers with high risk	9,668	85	8.3	6.7 to 10.3	94.1	87.0 to 97.5	88.5	87.9 to 89.2	6.8	5.5 to 8.4
First rounds	3,021	41	13.6	10.0 to 18.4	100	91.4 to 100	84.1	82.7 to 85.3	7.9	5.9 to 10.6
Subsequent rounds	6,647	44	5.9	4.3 to 8.0	88.6	76.0 to 95.0	90.6	89.8 to 91.2	5.9	4.3 to 8.0
< 30 years	481	0	0.0	0.0 to 7.9			93.6	91.0 to 95.4	0	0.0 to 11.0
30–39 years	2,089	6	2.9	1.3 to 6.3	100	61.0 to 100	90.2	88.8 to 91.4	2.8	1.3 to 6.1
40–49 years	3,254	28	7.4	5.0 to 11.0	85.7	68.5 to 94.3	89.7	88.6 to 90.7	6.8	4.6 to 9.9
≥ 50 years	823	10	10.9	5.8 to 20.7	90.0	59.6 to 98.2	93.1	91.2 to 94.7	13.8	7.5 to 24.3
Total	14,142	221	14.0	12.2 to 16.1	89.6	84.9 to 93.0	89.1	88.5 to 89.6	11.5	10.1 to 13.1

CI confidence interval, *PPV* positive predictive value

Bick U, Engel C, Krug B, et al. High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer. *Breast Cancer Res Treat*. 2019;175(1):217–228. doi:10.1007/s10549-019-05152-9

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 lifelong surveillance program				
▪ For detection of early stage breast cancers		2a	B	++
▪ 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)		3a	C	+/-*

* Follow-up care should be carried out as part of transparent quality assurance and appropriate evaluation.

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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 </= 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.**

	Oxford		
	LoE	GR	AGO
Currently, no specific surveillance is recommended			
▪ **For breast cancer: self examination and watchful waiting**	**5**	**D**	**+**
▪ **For prostate cancer: Compare recommendations on prostate carcinoma (https://www.prostatakrebs-bps.de/images/DGU-Stellungnahme_PSA_Pressemappe_2019.pdf)**	**3b**	**C**	**+**

* **Follow-up care /surveillance should be carried out as part of transparent quality assurance and appropriate evaluation.**

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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**

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Surgical Prevention

	Oxford		
	LoE	GR	AGO
▪ 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.	2a	B	+*

* study participation recommended

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

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	Oxford LoE	Oxford GR	AGO
▪ **Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)****	2a	B	
▪ Reduces OvCa incidence and mortality			++*
▪ Reduces overall mortality			++*
▪ **Risk-reducing bilateral mastectomy (RR-BM)**	2a	B	+*
▪ Reduces BC incidence	2b	B	+*
▪ Reduces BC mortality in *BRCA1* mutation carriers***			

* 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

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	Oxford LoE	Oxford GR	AGO
▪ Risk-reducing bilateral salpingo-oophorectomy (RR-BSO) ▪ Reduces OvCa incidence and mortality ▪ Reduces overall mortality (contradictory results for reduction of cl BC incidence)	2b	B	+*
▪ Prophylactic contralateral mastectomy (RR-CM) ▪ Reduces BC incidence and mortality	2b	B	+*
▪ Tamoxifen (reduces contralateral BC incidence)	2b	B	+/-*
▪ Indication for RR-M should consider age at onset of first breast cancer in affected gene	2a	B	++*
▪ RR-M 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

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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.

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

	Oxford LoE	GR	AGO
▪ Breast conserving surgery: adequate local tumor control (~10 years observation)	2a	B	+
▪ Systemic therapy according to sporadic breast cancer	3a	B	+
▪ gBRCA mutation status is predictive for chemotherapy response in TNBC	2b	B	+
▪ Carboplatin (vs. Docetaxel) in metastatic breast cancer	2b	B	+
▪ PARP inhibitor in metastatic breast cancer	1b	B	+

Medical Prevention for Women at Increased Risk

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	Oxford		
	LoE	GR	AGO
▪ Tamoxifen for women >35 years: reduction of invasive BC, DCIS, and LN	1a	A	+*
▪ Raloxifen for postmenopausal women: reduction of invasive BC only	1b	A	+*
▪ AI for postmenopausal women	1b	A	+#

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)

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Risk Reduction for Ipsi- and Contralateral Breast Cancer

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

	Oxford		
	LoE	GR	AGO
▪ Tamoxifen*	1a	A	+
▪ Aromatase inhibitors*	1a	A	+
▪ Suppression of ovarian function* + Tamoxifen	1b	B	+

* 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*

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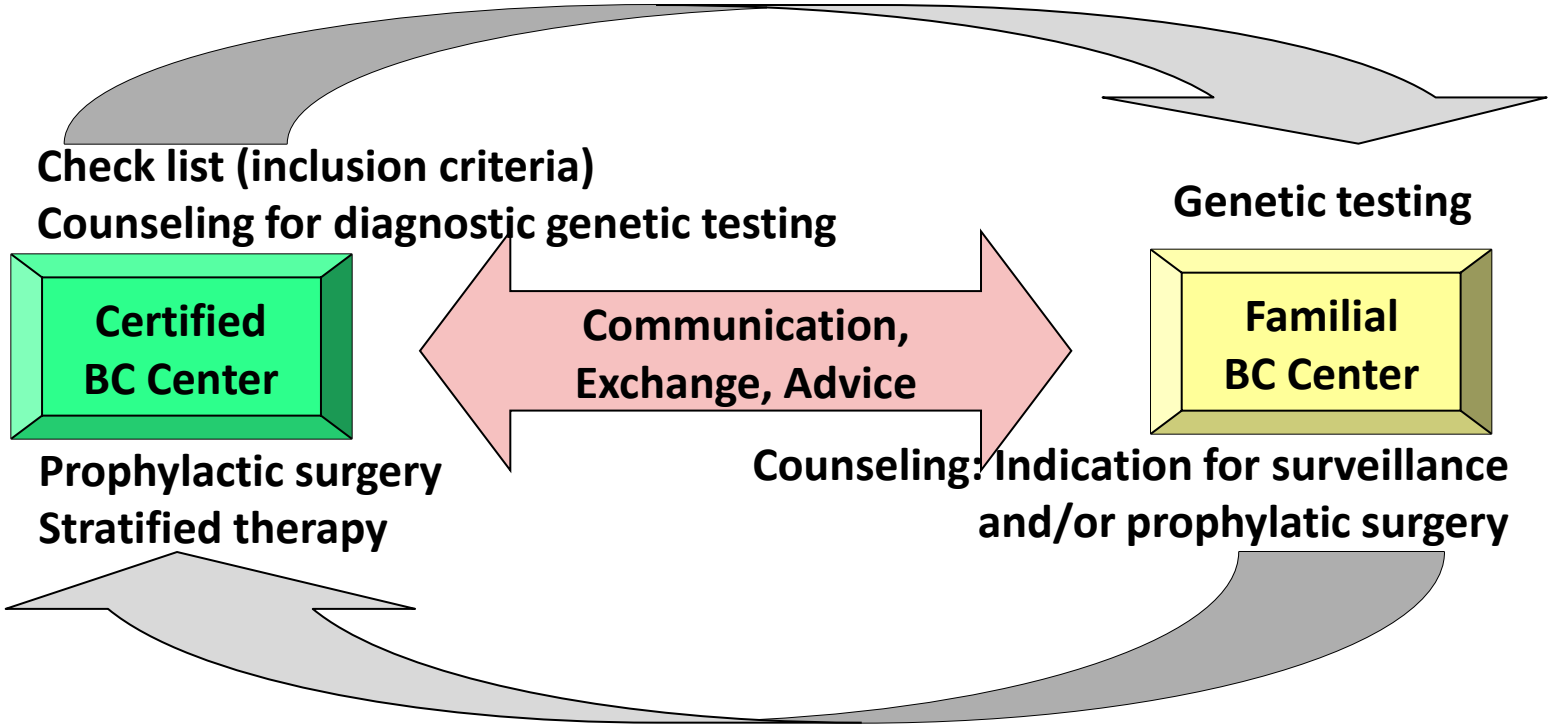

* trans-sectoral contract for integrated care, acc. to code of social law § 140a since 2015