Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2019.1

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Breast Cancer Risk and Prevention

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Breast Cancer Risk and Prevention

- **Versions 2003–2018:**
  Schmutzler with Albert / Blohmer / Fasching / Fehm / Kiechle / Maass / Mundhenke / Riehm / Rody / Schmidt / Stickeler / Thomssen

- **Version 2019:**
  Ditsch / Müller-Schimpfle / Bischoff

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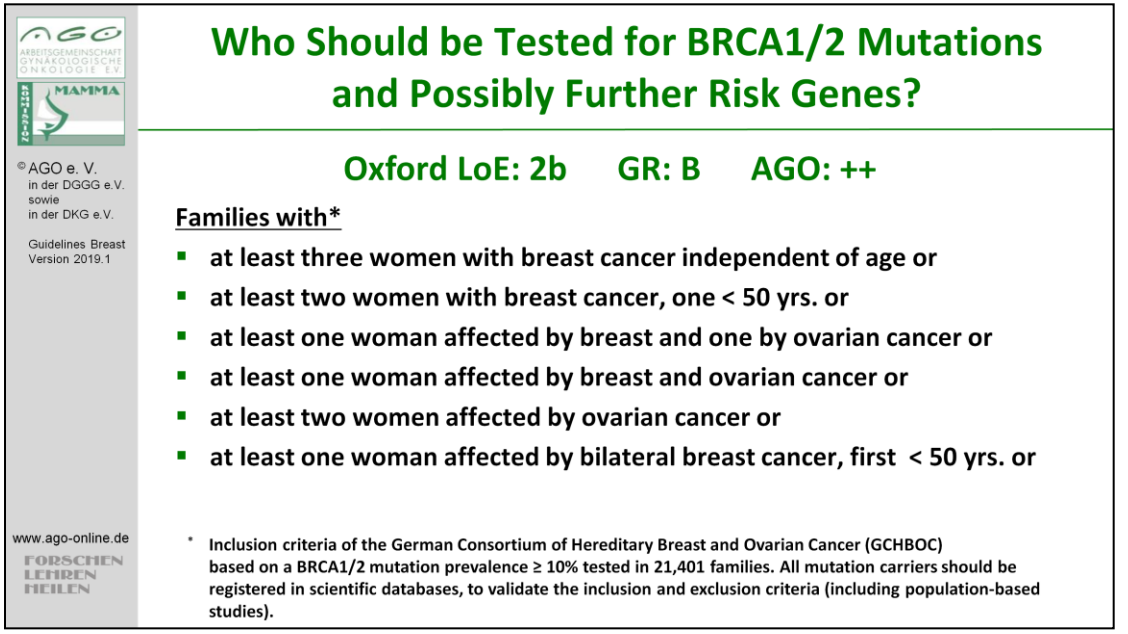
Principles of Prevention

- **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)



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7. Harter P, Hauke J, Heitz F, et al. Prevalence of deleterious germline variants in risk genes including BRCA1/2 in consecutive ovarian

cancer patients (AGO-TR1). PLoS One 2017;12:e0186043. - neu

8. Engel C, Rhiem K, Hahnen E, et al. Prevalence of pathogenic BRCA1/2 germline mutations among 802 women with unilateral triple-negative breast cancer without family cancer history. BMC Cancer BCA-D-17-00805R2 (in revision) - neu
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11. Couch FJ, Hu C, Hart SN et al.: Age-related breast cancer risk estimates for the general population based on sequencing of cancer predisposition genes in 19,228 breast cancer patients and 20,211 matched unaffected controls from US based cohorts in the CARRIERS study GS2-01, oral presentation, SABCS 2018
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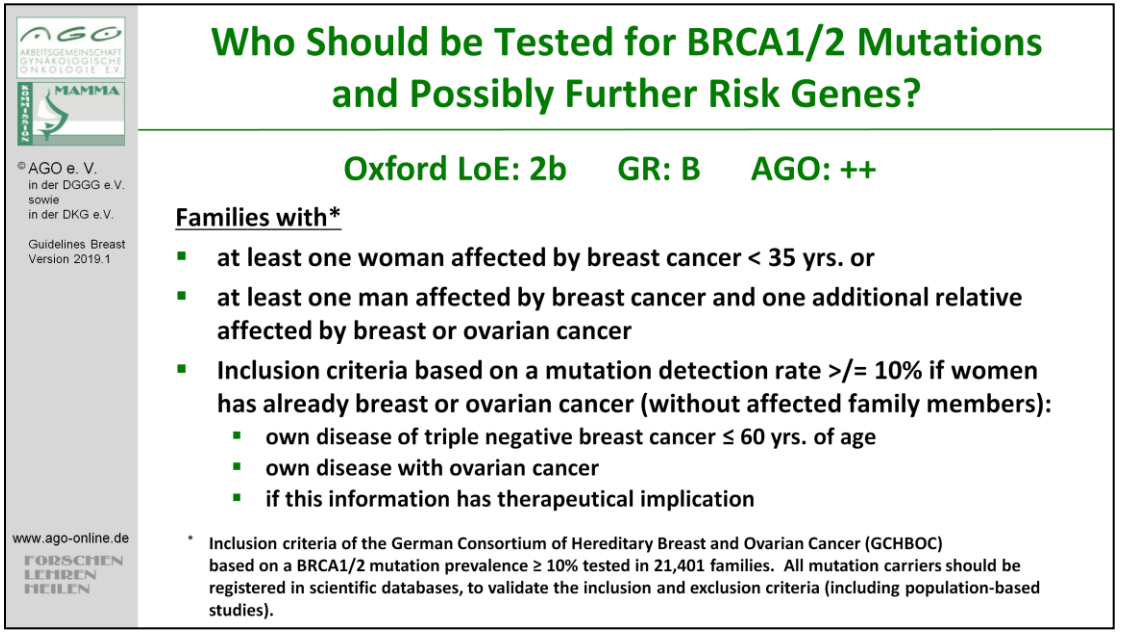

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Checklist according to Public Health Insurance Policies (German GKV)*

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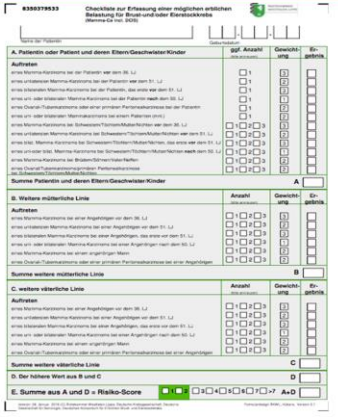

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Checkliste zur Erfassung einer möglichen erblichen Belastung für Brust-und oder Eierstockkrebs
(Mamma-Ca incl. DCIS)

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	1	
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	4	
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 (m/w)	☐ 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	4	
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	4	
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	4	
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	☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ >7		A+D

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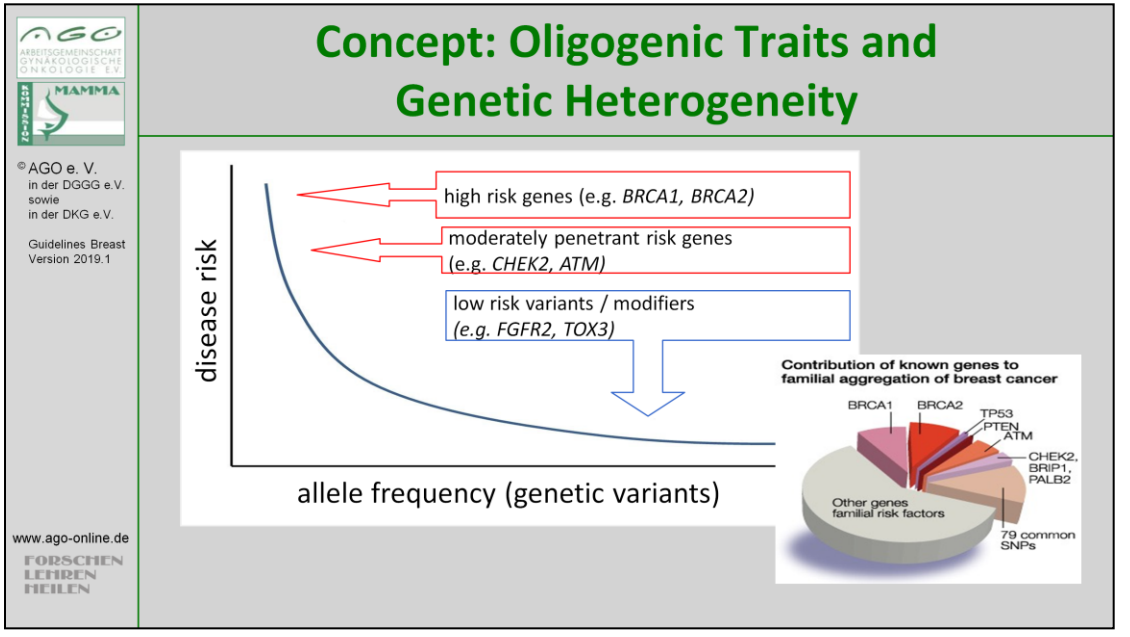
* online tool provided by the Ärztekammer Westfalen-Lippe in cooperation with the GC-HBOC based on the inclusion criteria of the GC-HBOC (Kast et al., J Med Genet 2016;53:465-71), http://www.aekwl.de/fileadmin/qualitaetssicherung/Zertifizierungsstelle/FB-erbliche_Belastung_V2016-01-06.pdf



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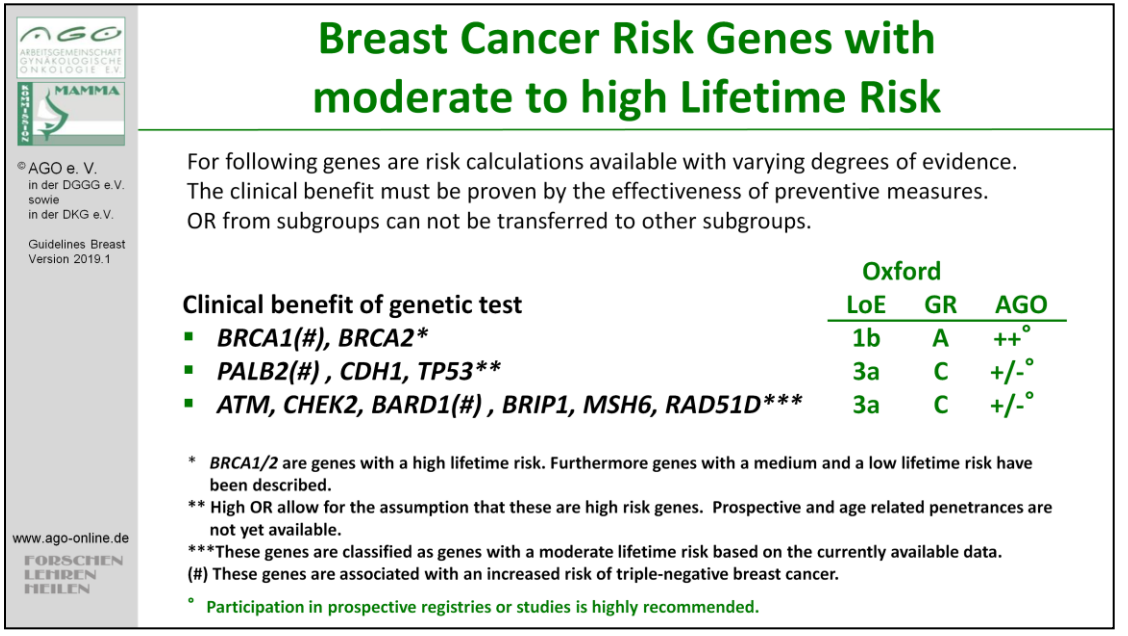

Breast Cancer Risk Genes with moderate to high Lifetime Risk

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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	Oxford LoE	GR	AGO
▪ *BRCA1(#), BRCA2**	1b	A	++°
▪ *PALB2(#) , CDH1, TP53***	3a	C	+/-°
▪ *ATM, CHEK2, BARD1(#) , BRIP1, MSH6, RAD51D****	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.
(#) 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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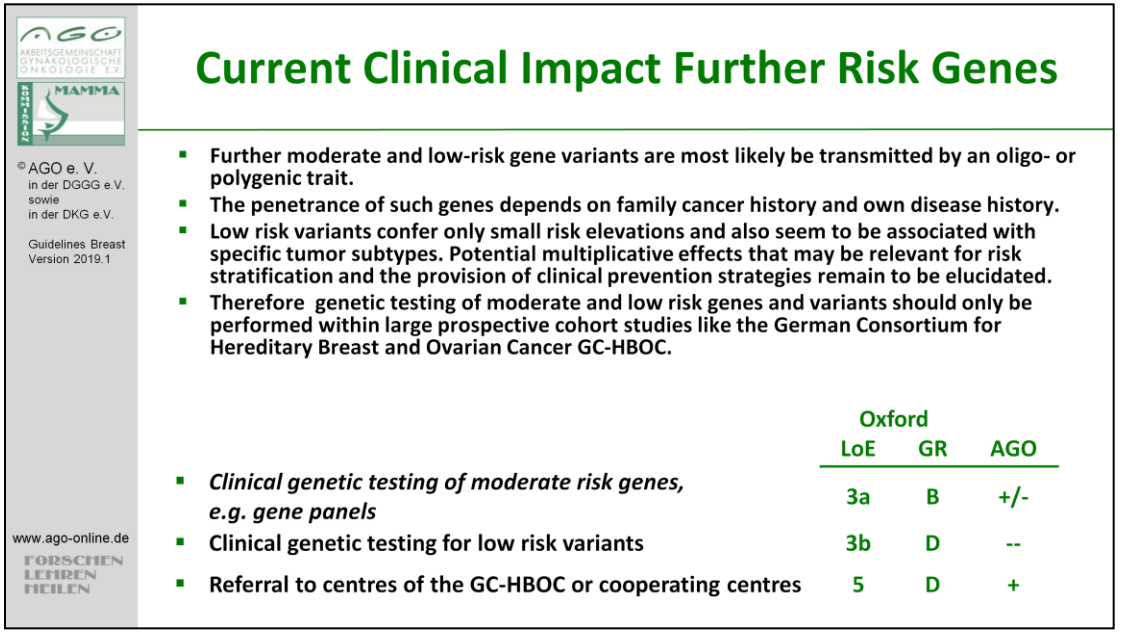

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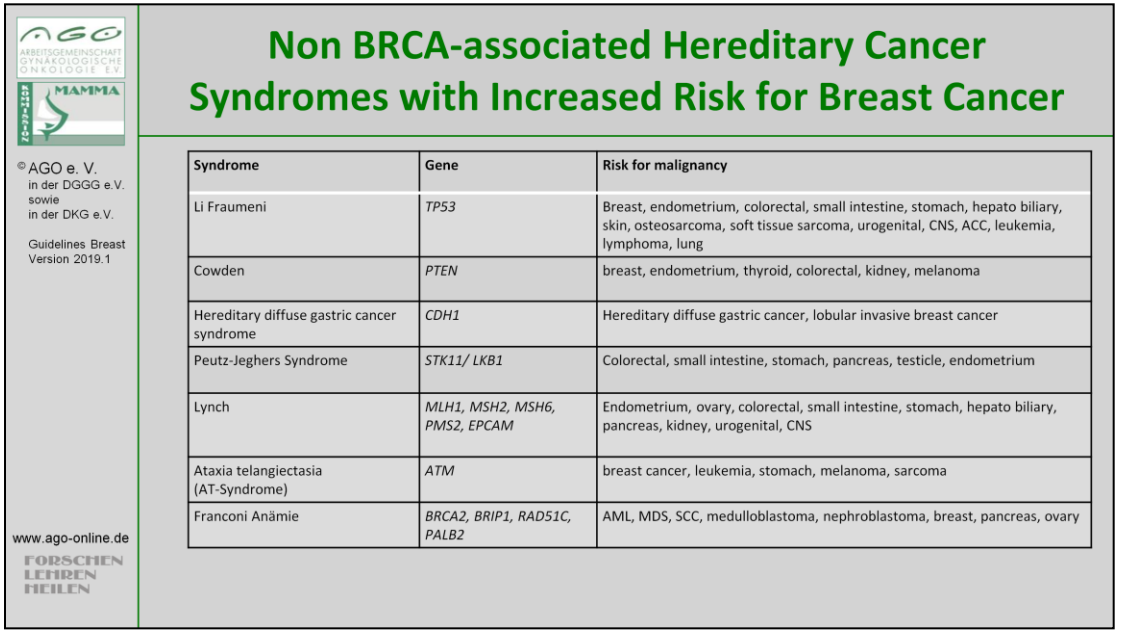

Syndrome	Gene	Risk for malignancy
Li Fraumeni	*TP53*	Breast, endometrium, colorectal, small intestine, stomach, hepato biliary, skin, osteosarcoma, soft tissue sarcoma, urogenital, CNS, ACC, leukemia, lymphoma, lung
Cowden	*PTEN*	breast, endometrium, thyroid, colorectal, kidney, melanoma
Hereditary diffuse 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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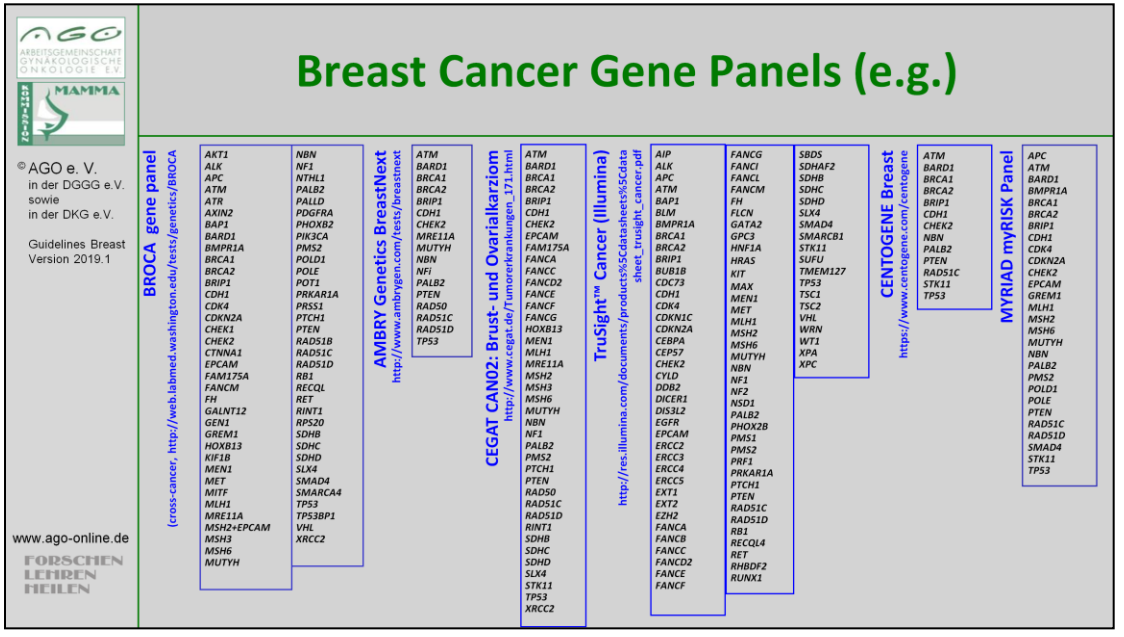

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TruRisk® BC/OC Gene Panel (34 genes) by the German Consortium GC-HBOC

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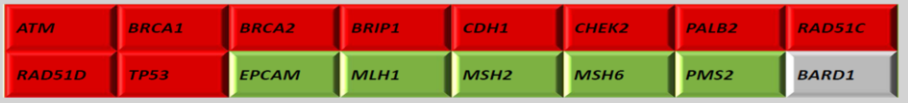
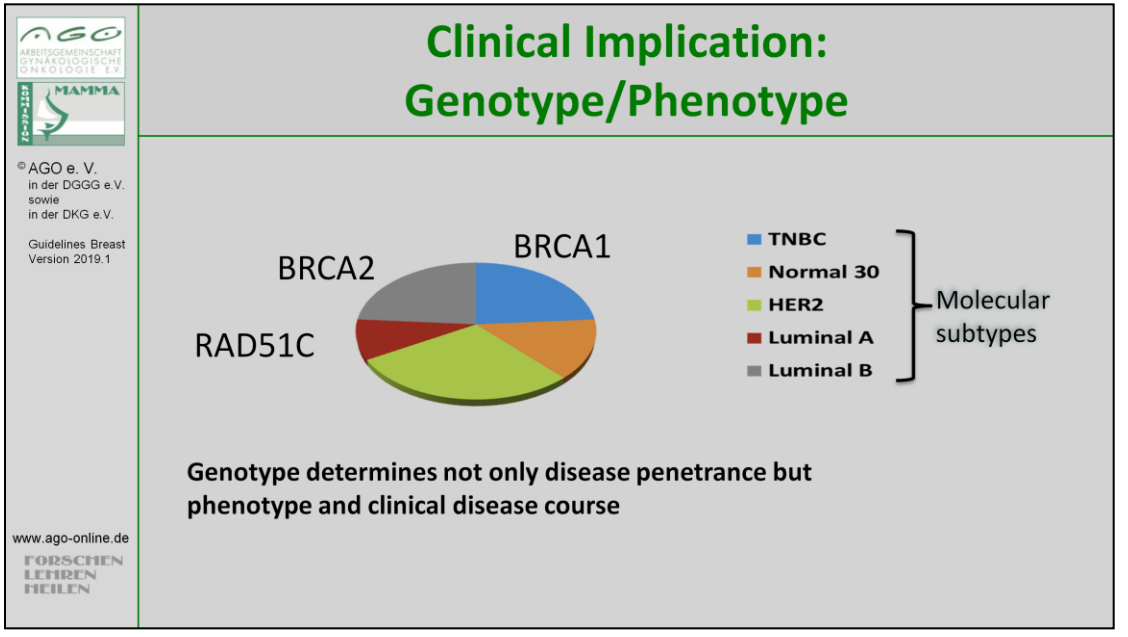


Gene selection: **10 BC/OC ‚core genes'** (sufficiant data for genetic counseling)
5 HNPCC genes
further syndromic genes (Cowden, Peutz-Jeghers)
19 BC/OC genes as part of scientific validation

Strategy:

- **Validation in large cohort, constant expansion and improvement**



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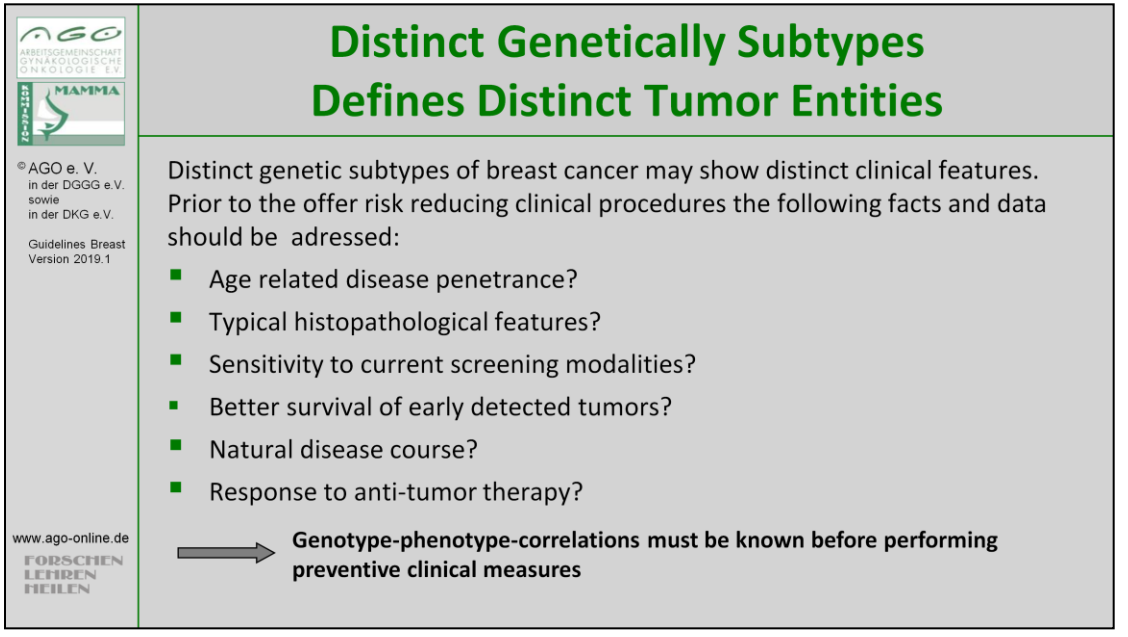

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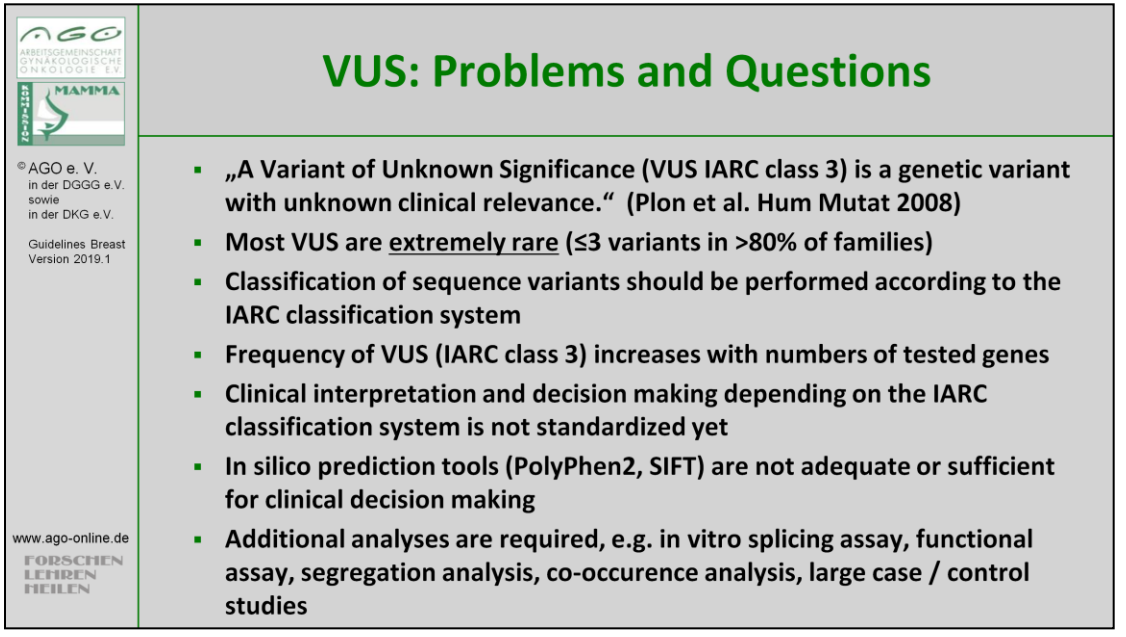

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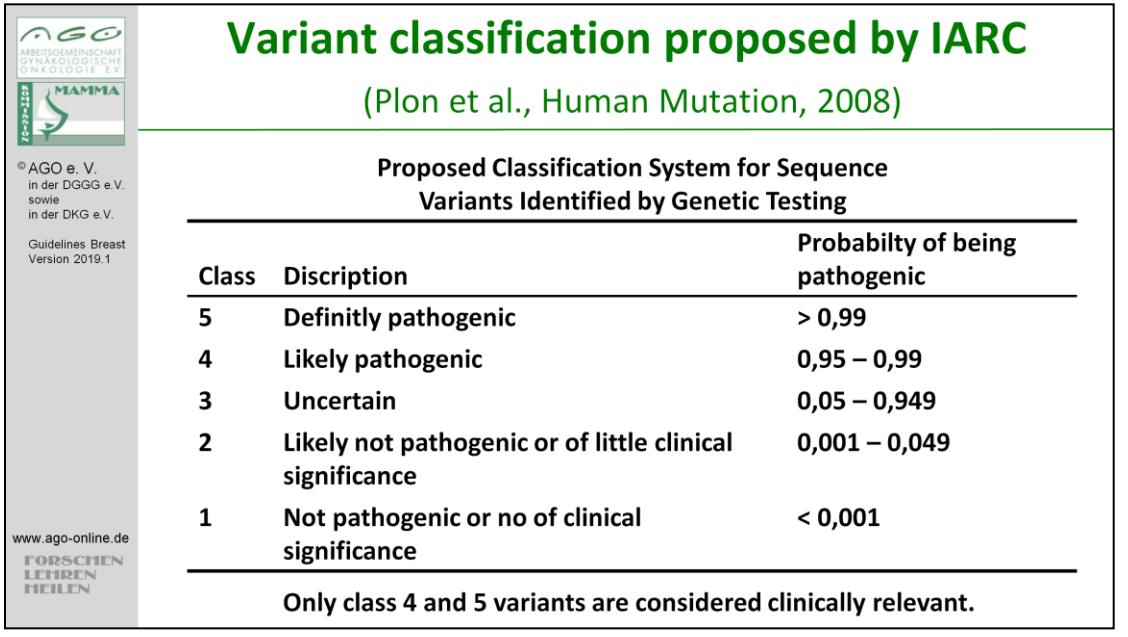

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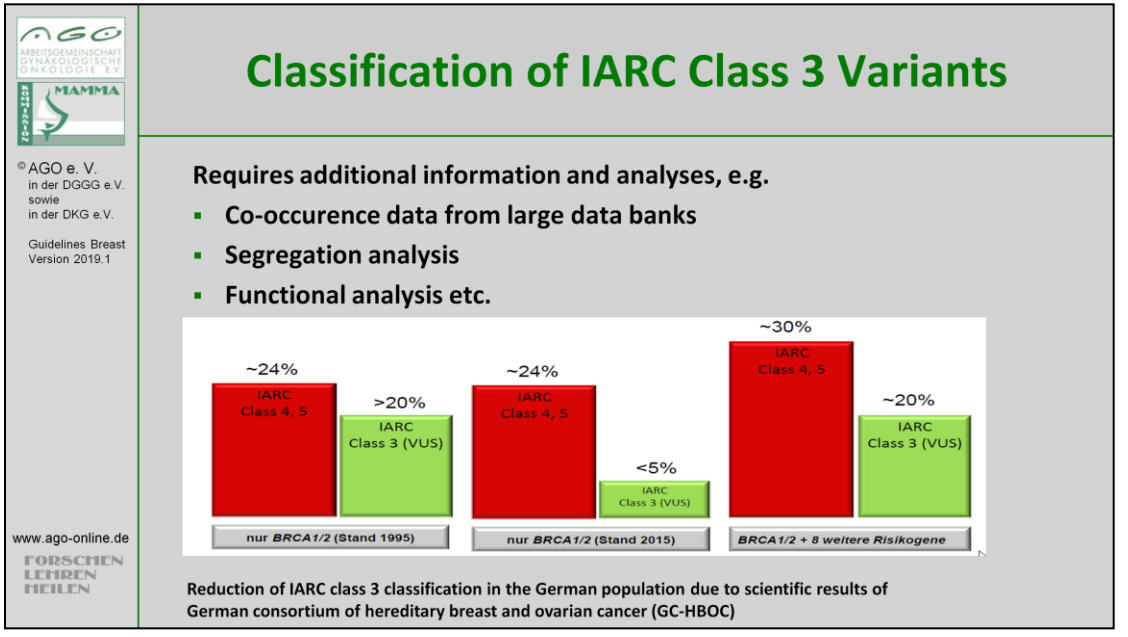

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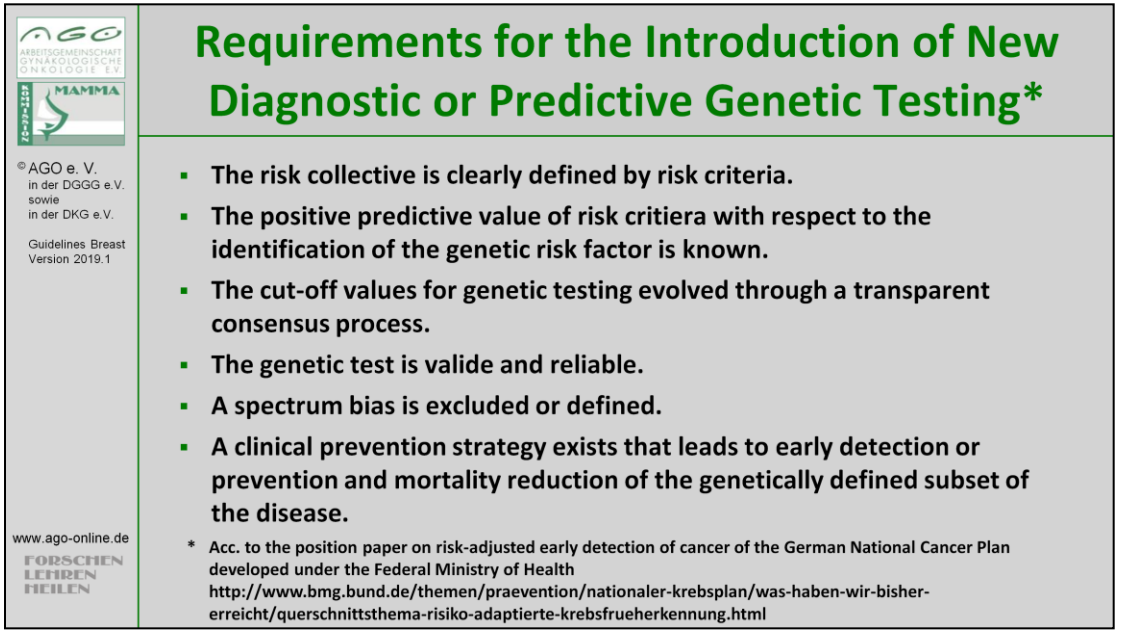

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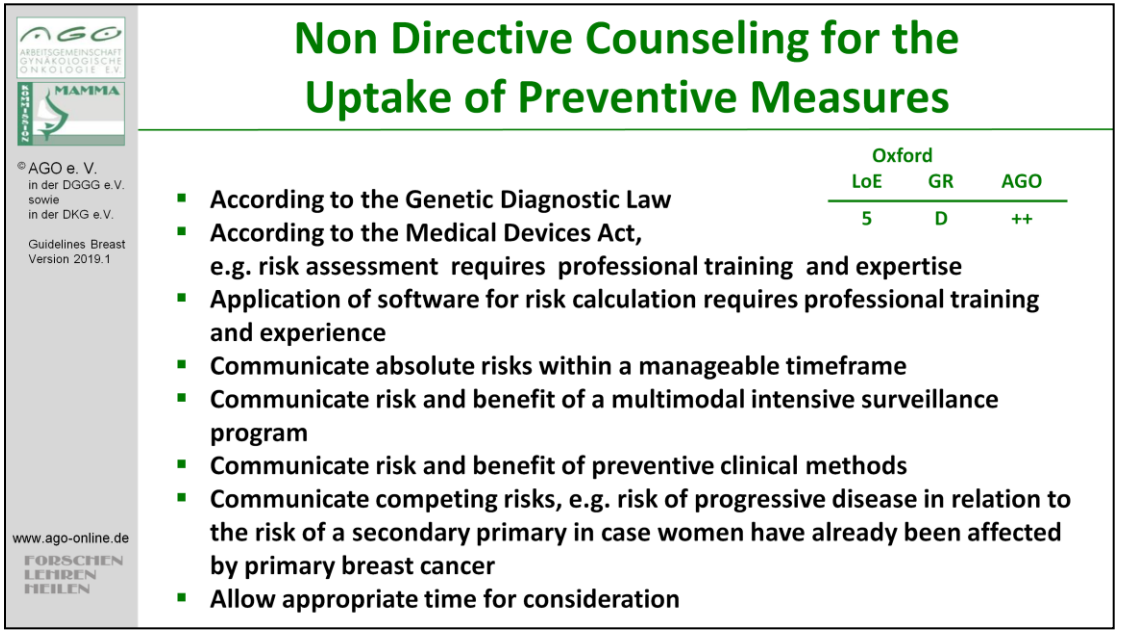

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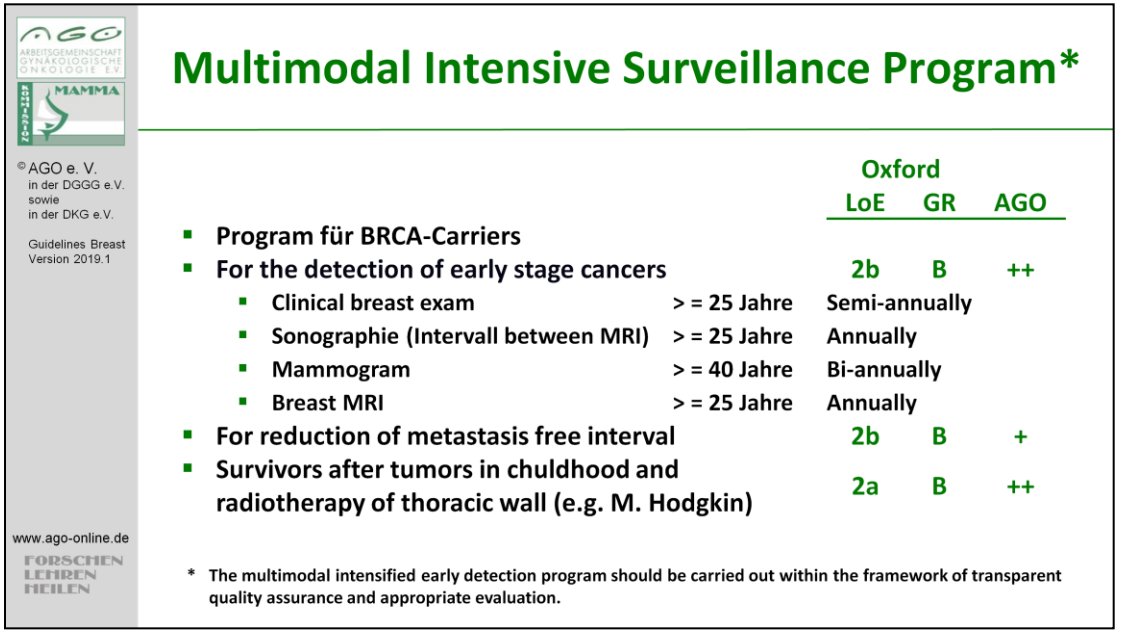

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High risk screening including MRI

- 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., Endel 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, accepted

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Table 6. 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 ‰	95% CI	Sensitivity %	95% CI	Specificity %	95% CI	PPV %	95% CI
BRCA1-carriers	2,760	83	26.6	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	76.5 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	679	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	90.6 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	3,264	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

Abbreviations: CI, confidence interval; PPV, positive predictive value

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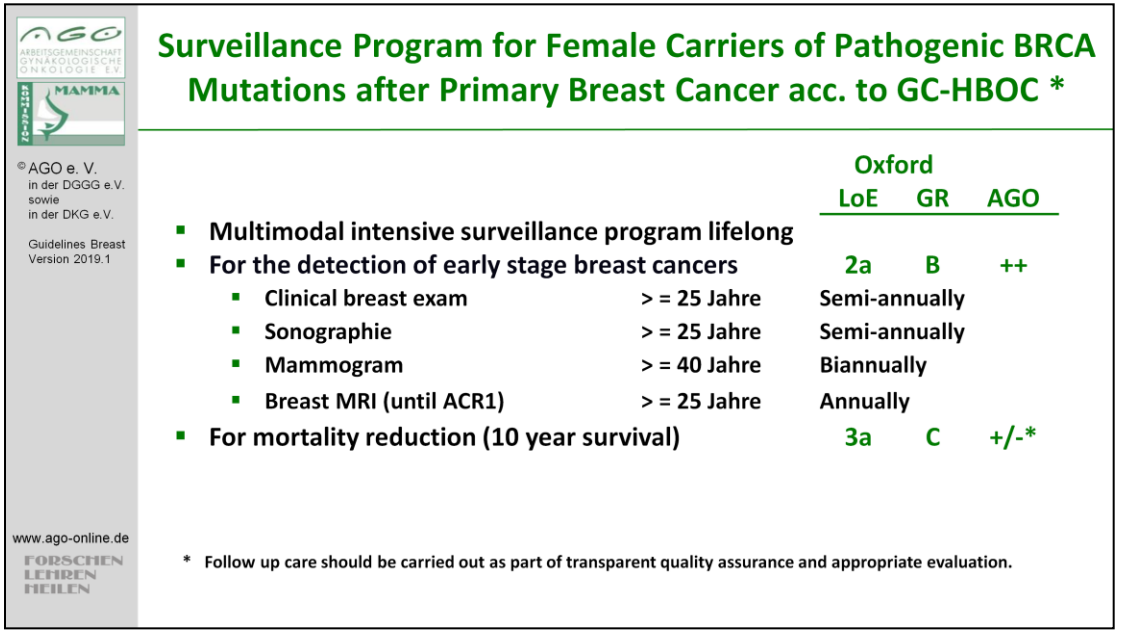

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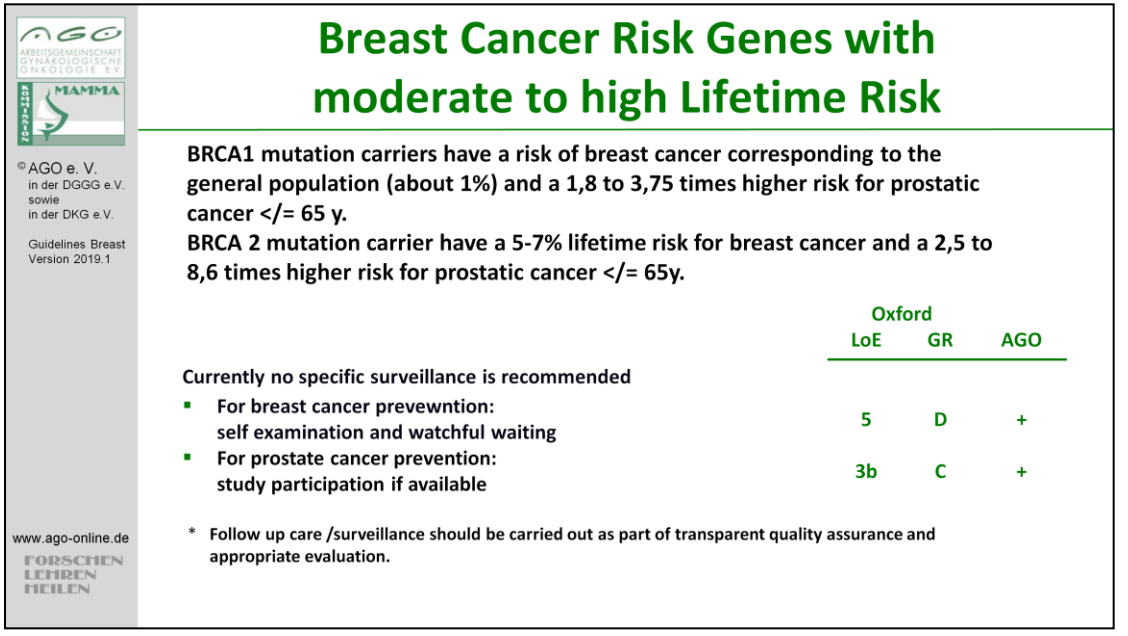

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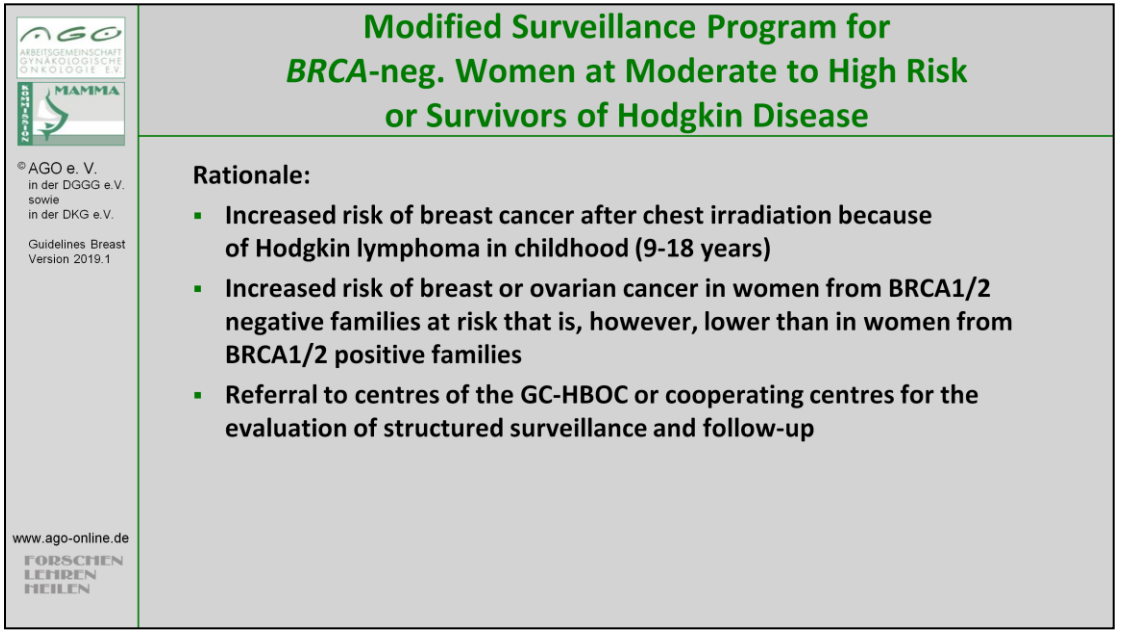

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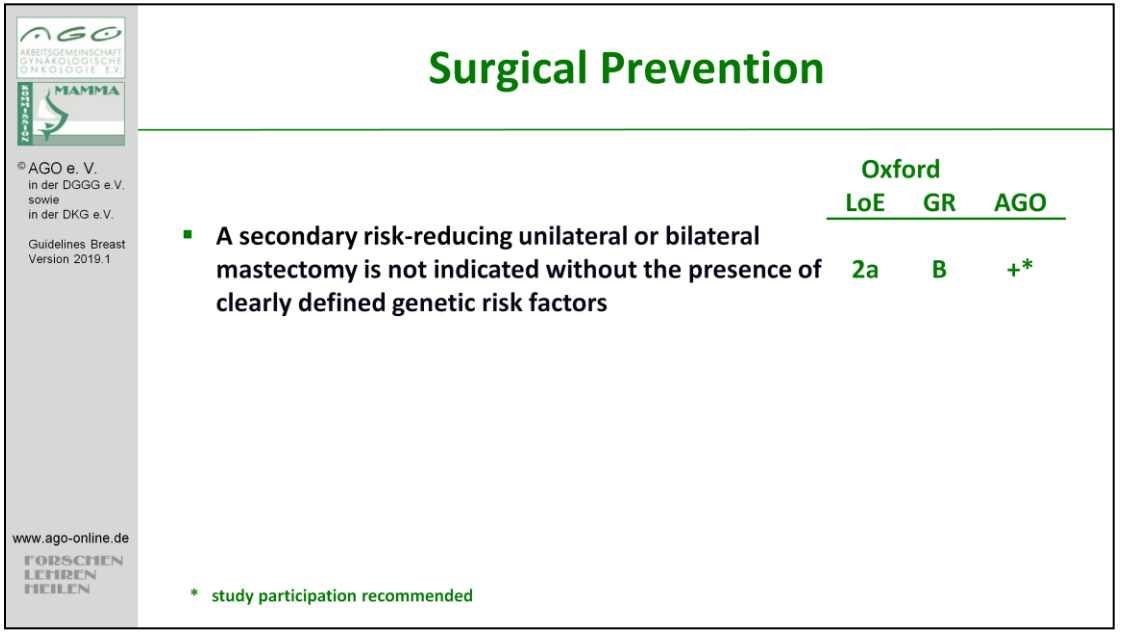

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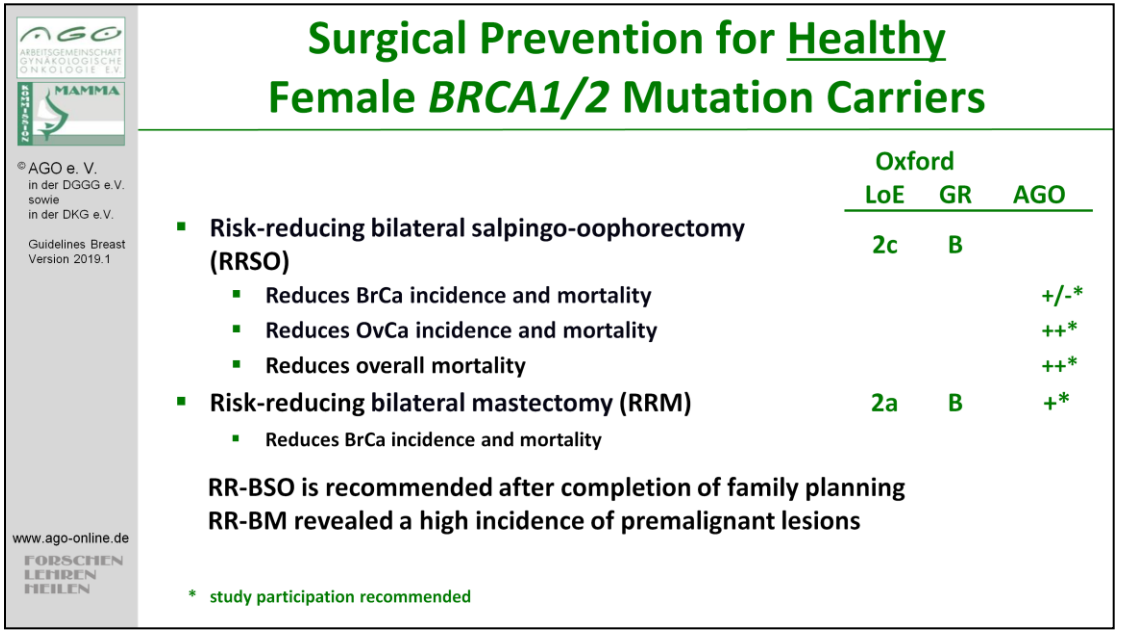

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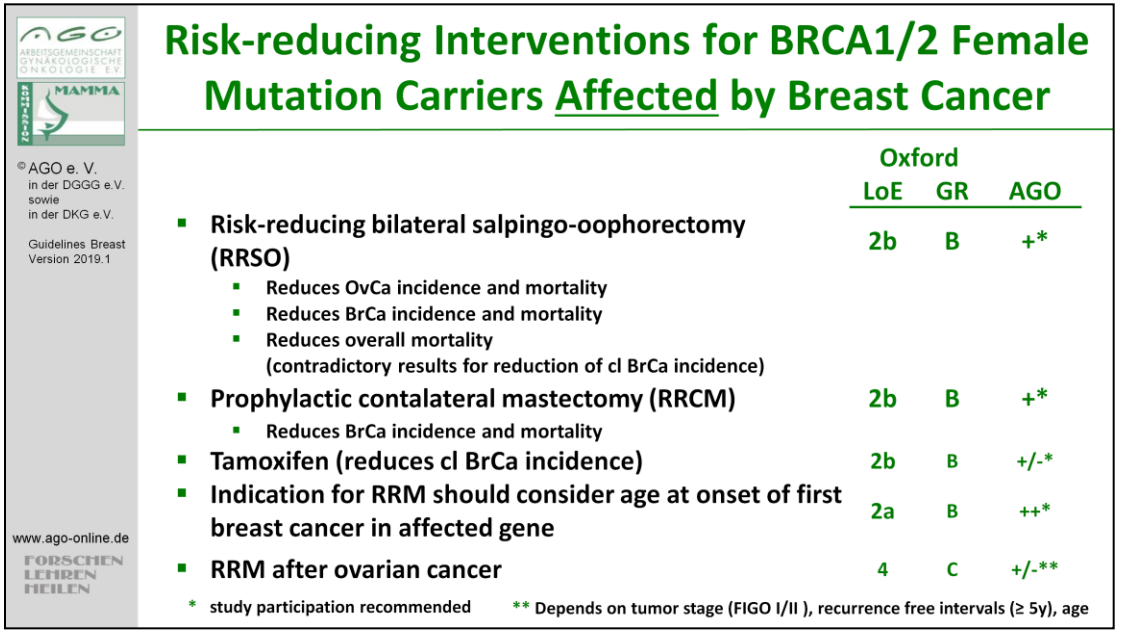

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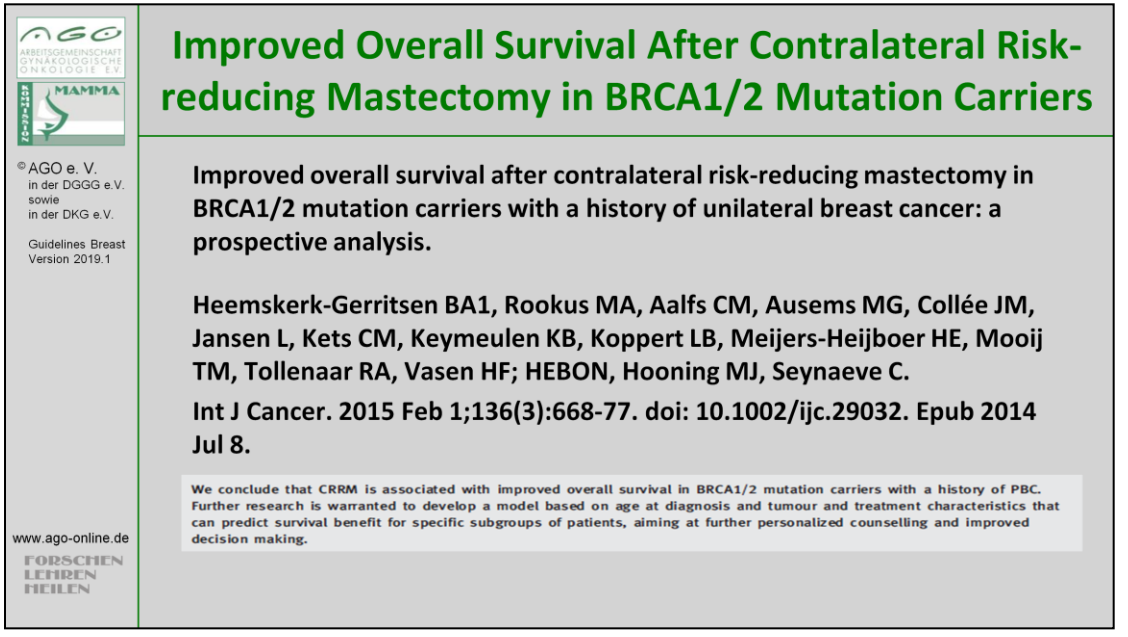

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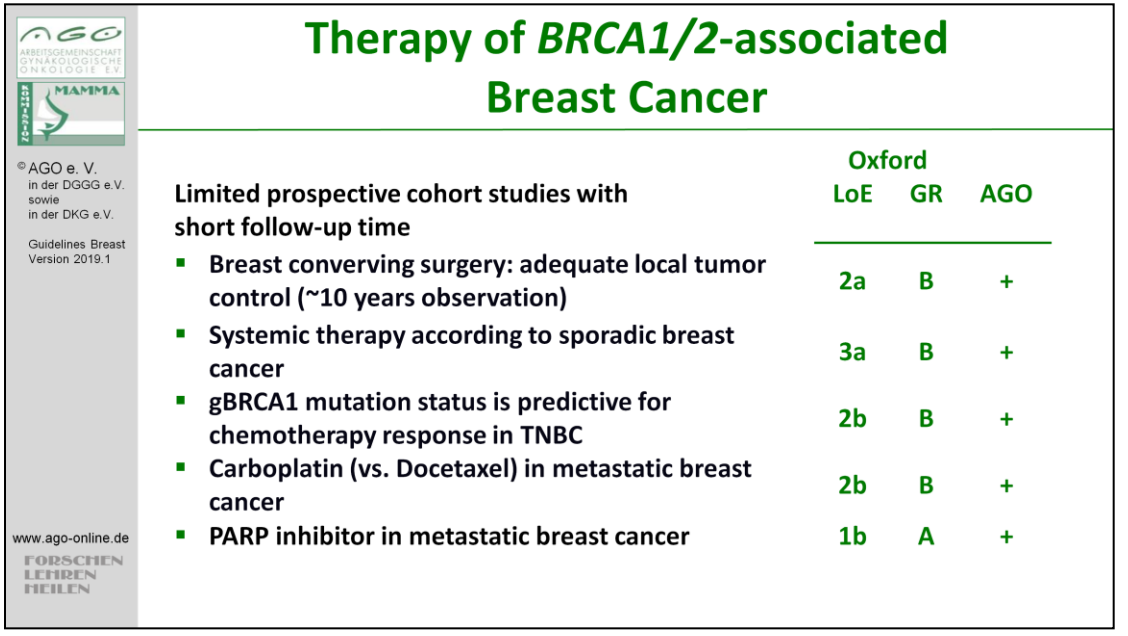

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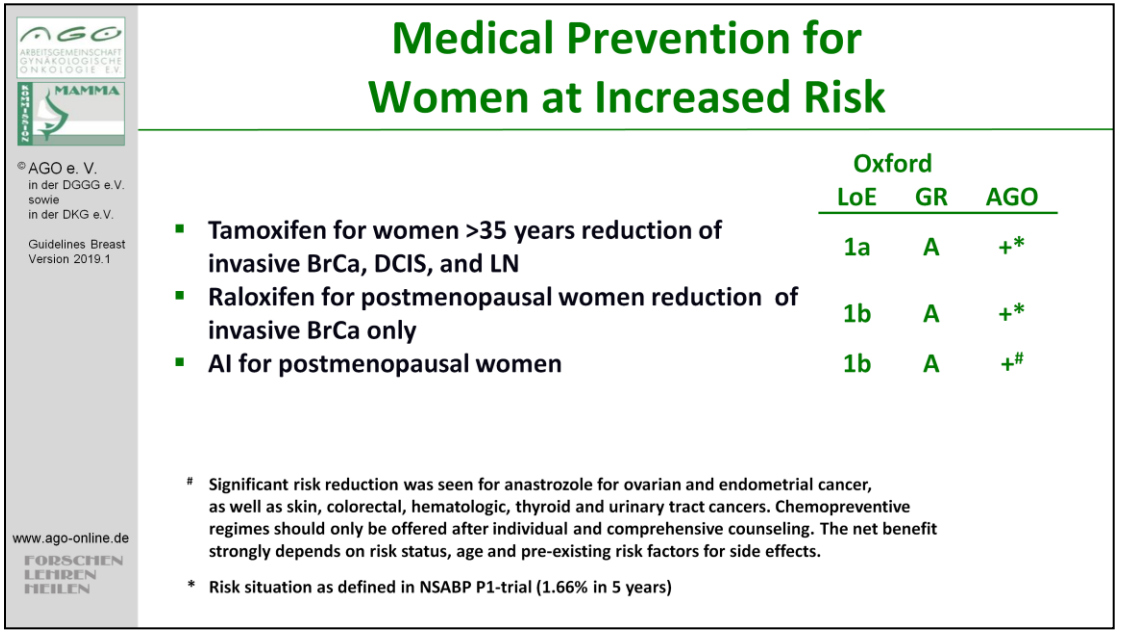
SABCS:

Robson - OlympiaD

Litton SABCS - EMBRACA



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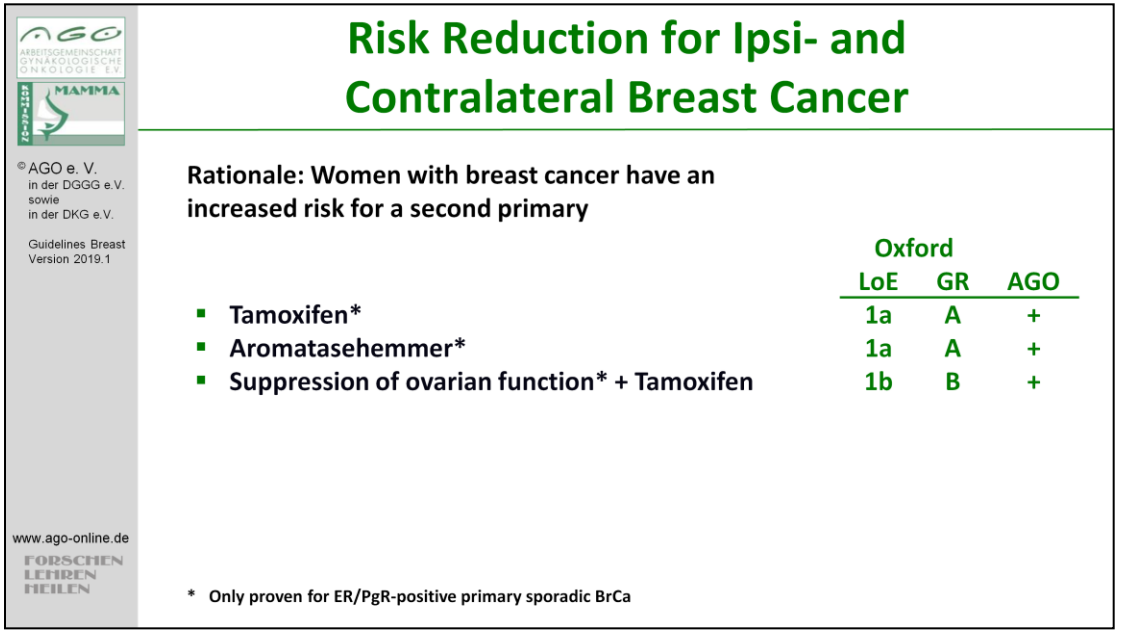

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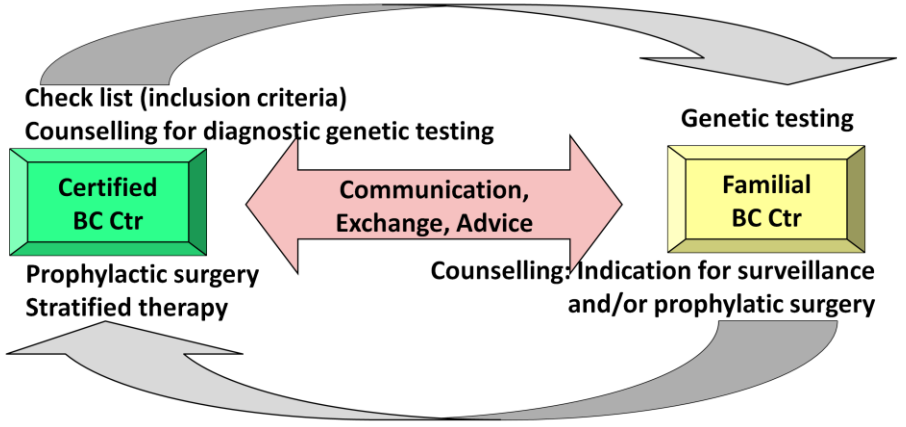

* trans-sectoral contract for integrated care, acc. to code of social law § 140a since 2015