Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2020.1

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Breast Cancer Risk and Prevention

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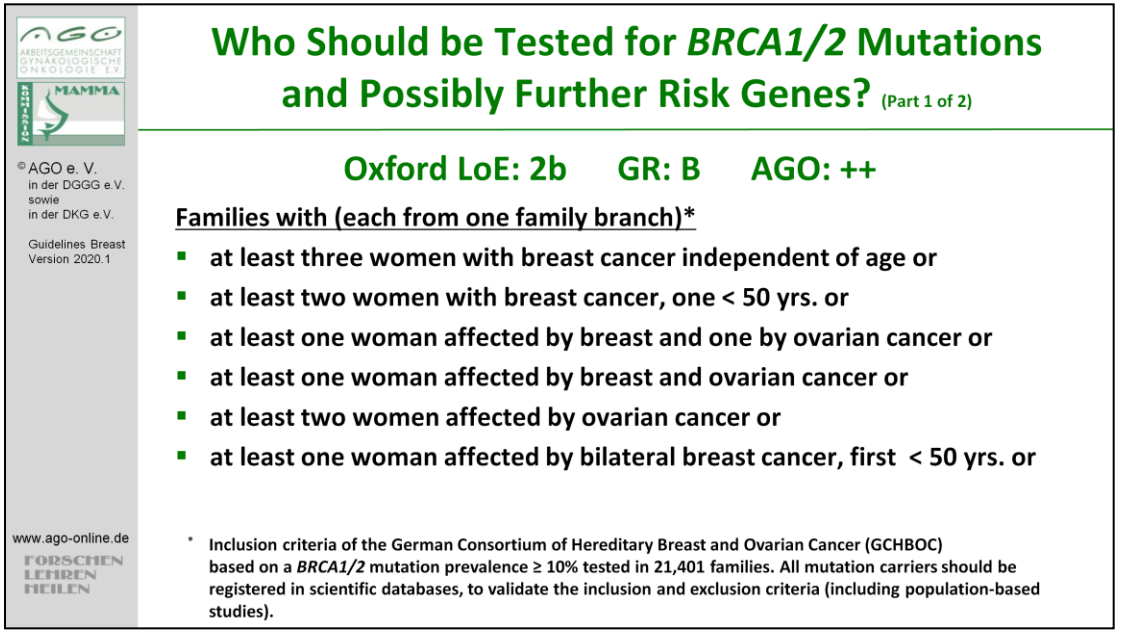
- **Versions 2003–2019:**
  Schmutzler mit Albert / Bischoff / Blohmer / Ditsch / Fasching / Fehm / Kiechle / Maass / Müller-Schimpfle / Mundhenke / Rhiem / Rody / Schmidt / Schmutzler / Stickeler / Thomssen /

- **Version 2020:**
  Fasching / Rhiem

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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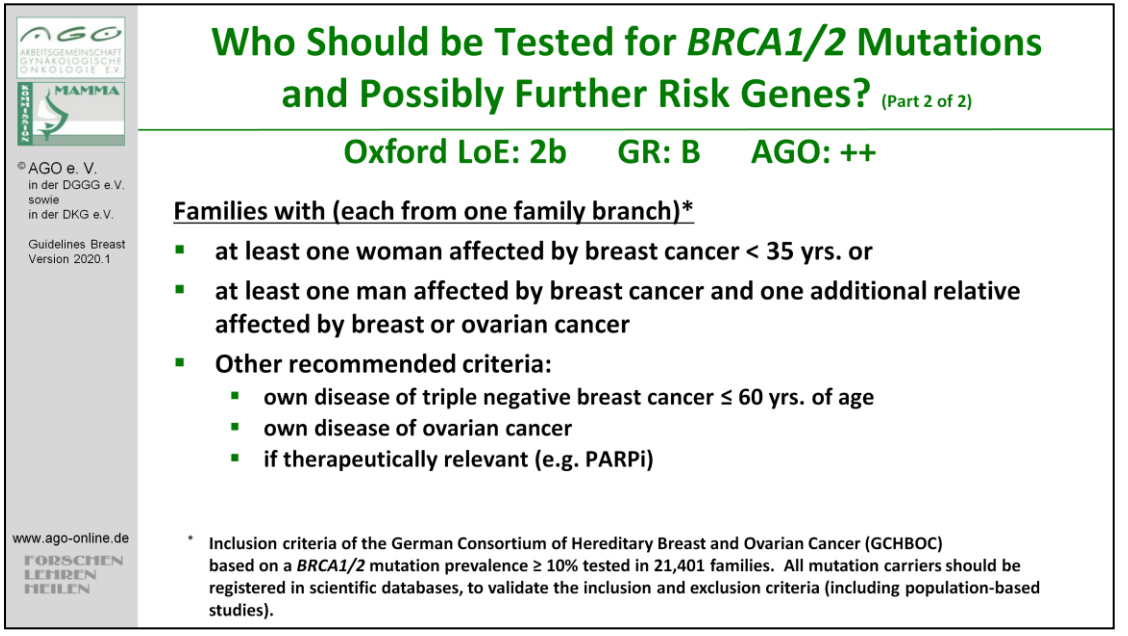

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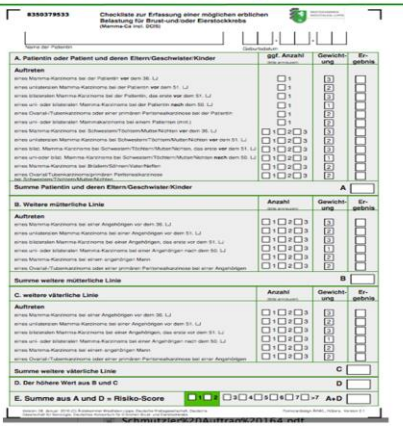
Checklist according to Public Health Insurance Policies (German GKV#)*



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

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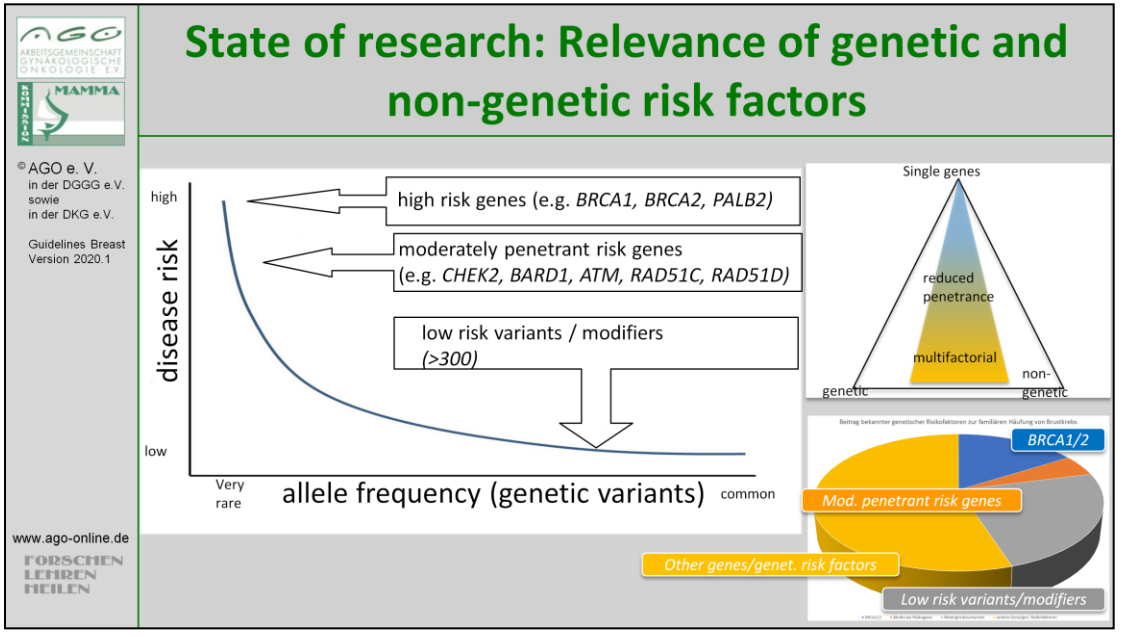

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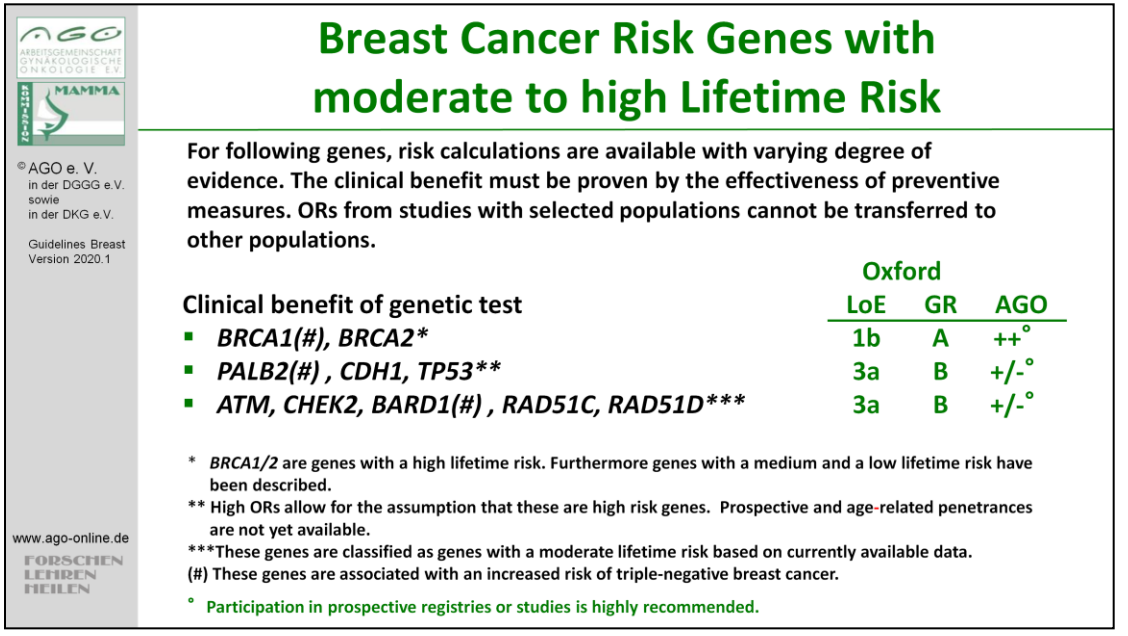

Breast Cancer Risk Genes with moderate to high Lifetime Risk

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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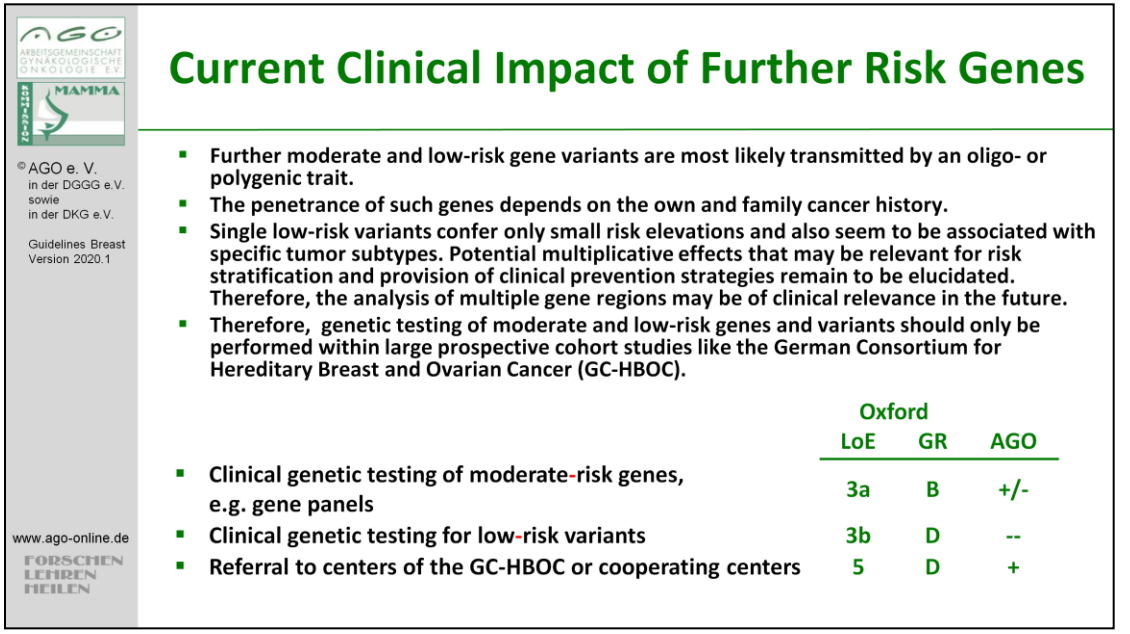

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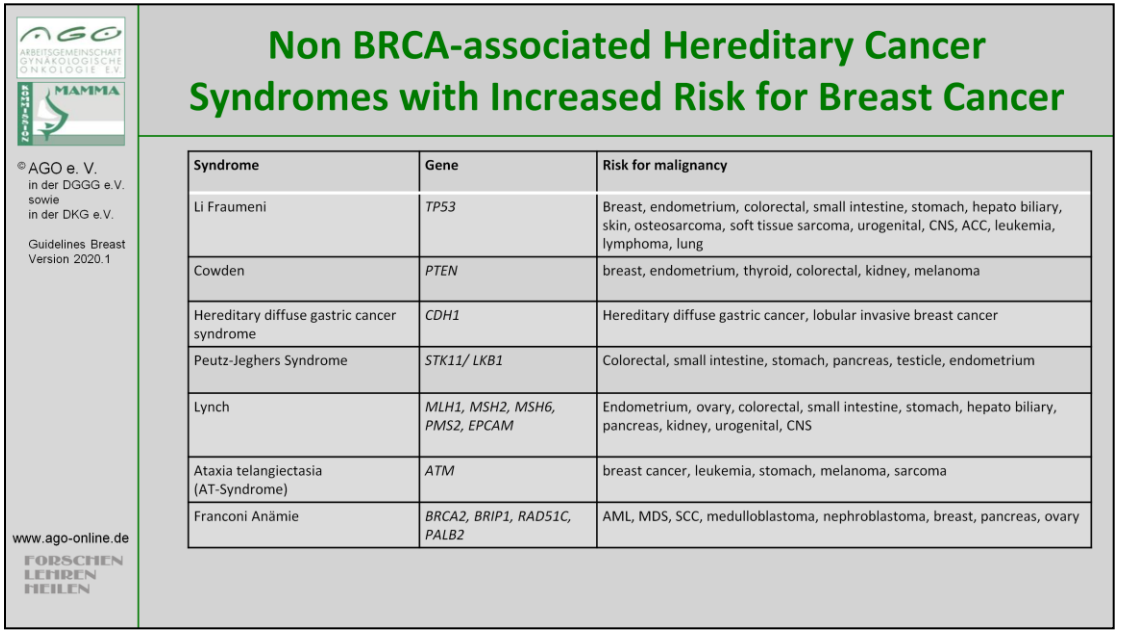

Non BRCA-associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer

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)

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ATM	*BARD1*	*BRCA1*	*BRCA2*	*BRIP1*	*CDH1*	*CHEK2*	*PALB2*
RAD51C	*RAD51D*	*TP53*	*EPCAM*	*MLH1*	*MSH2*	*MSH6*	*PMS2*
PTEN	*STK11*	*APC*	*FAM175A*	*FANCC*	*FANCM*	*HOXB13*	*MEN1*
MRE11A	*MUTYH*	*NBN*	*NF1*	*POLD1*	*POLE*	*RAD50*	*RECQL*
SMARCA4	*XRCC2*						

Selection of genes:
11 BC/OC '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

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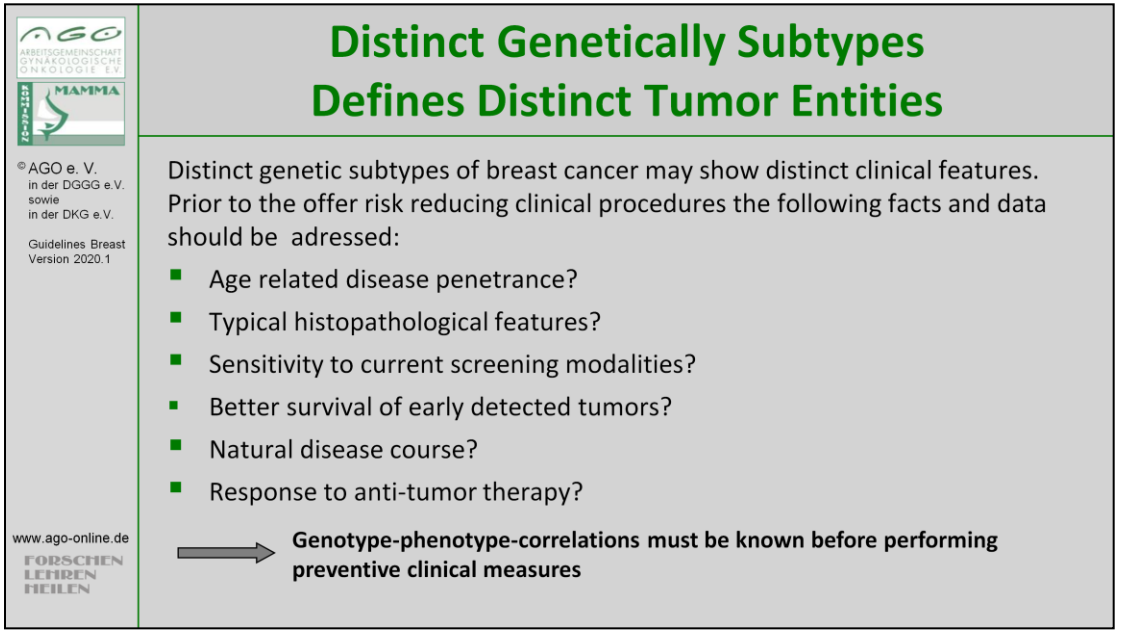

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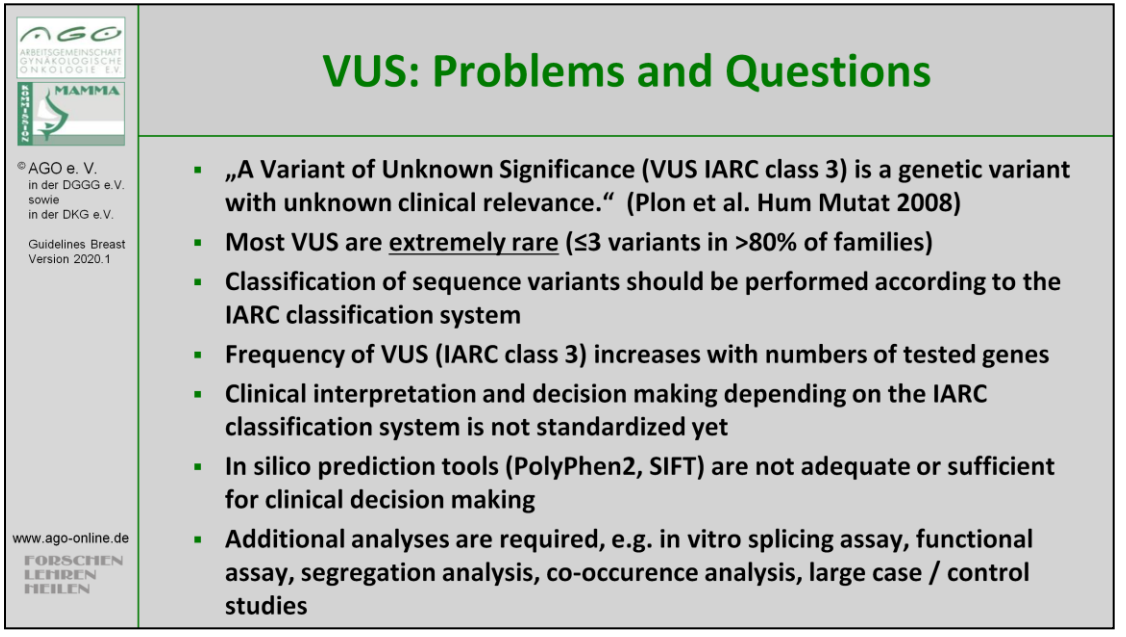

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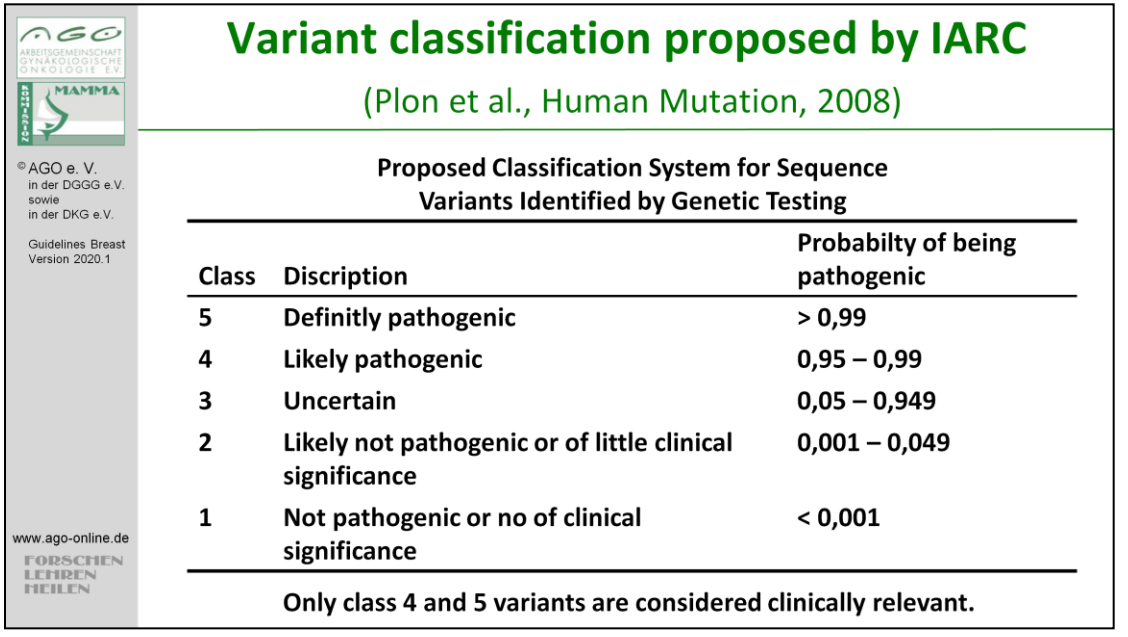

Variant classification proposed by IARC

(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.

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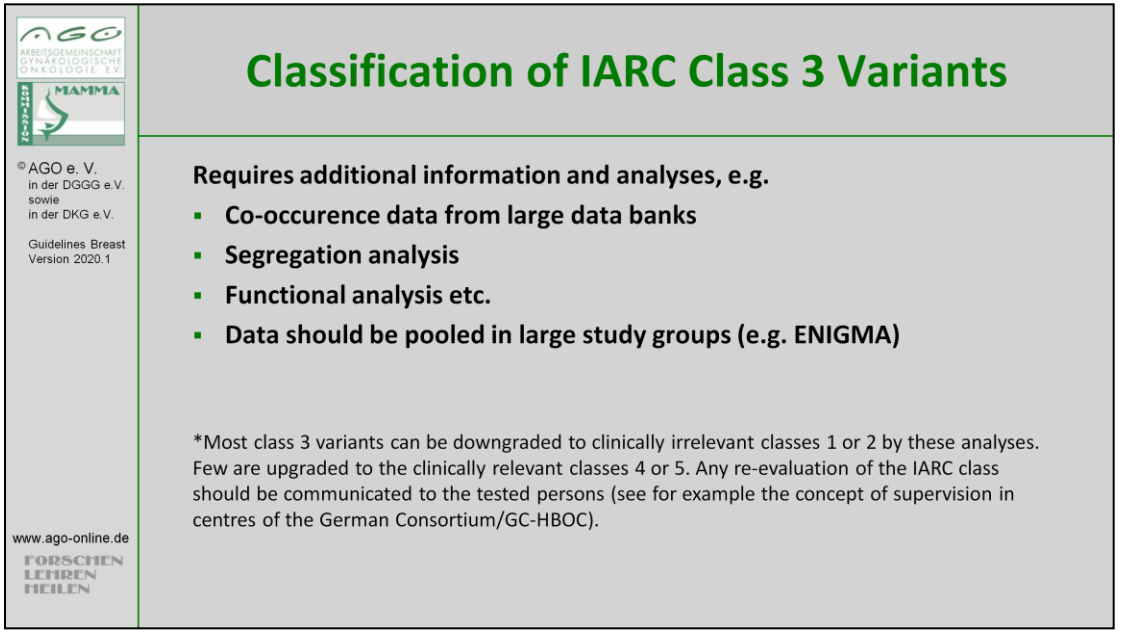

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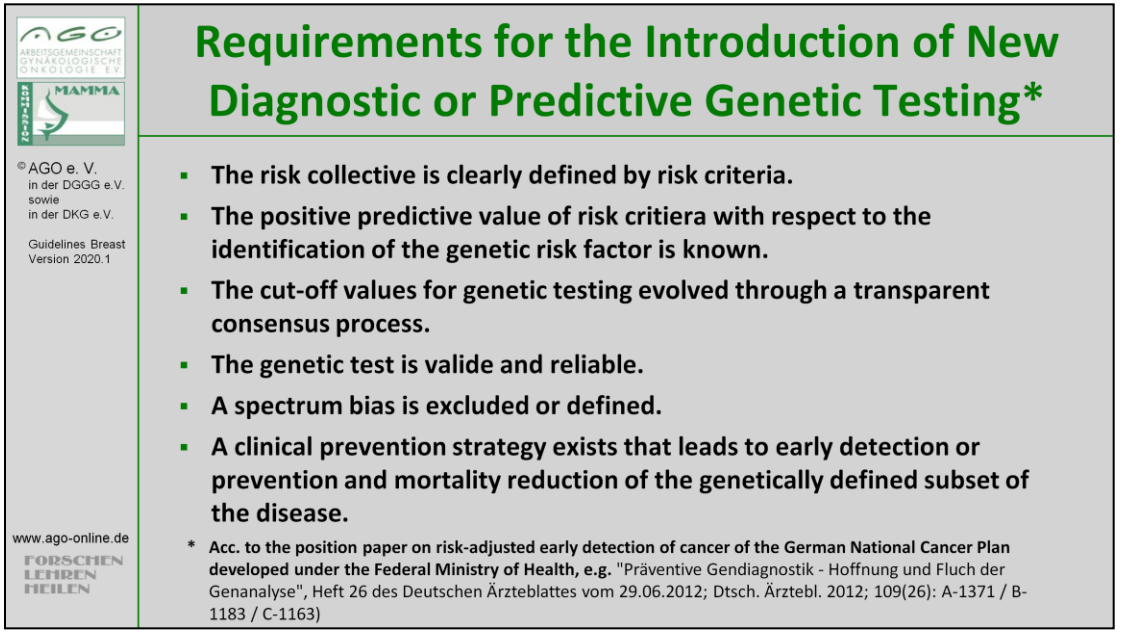

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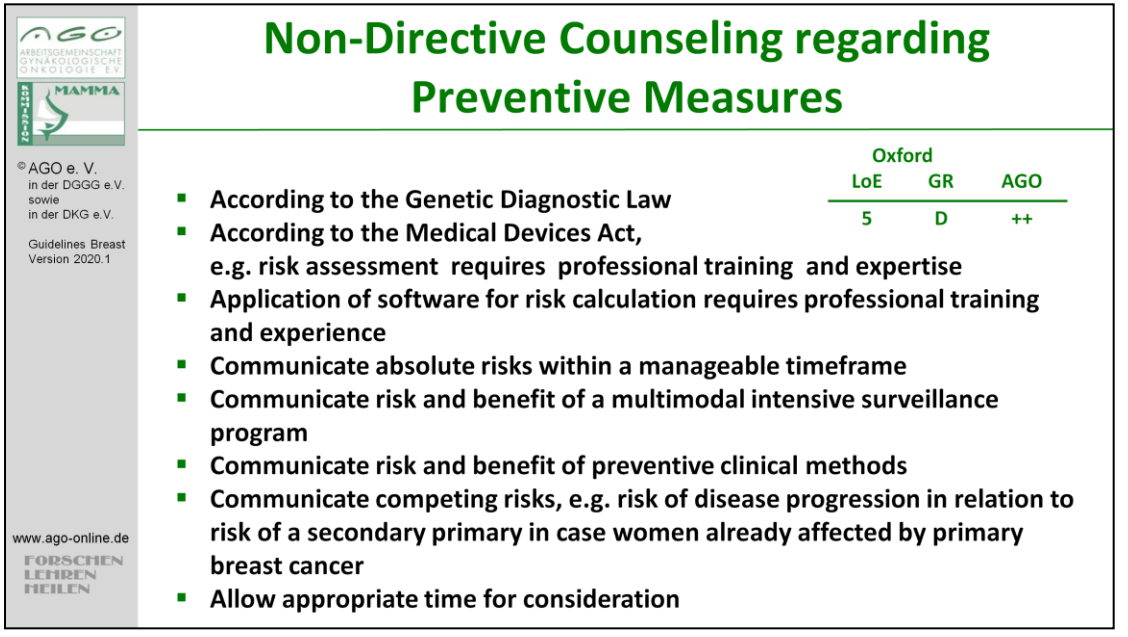

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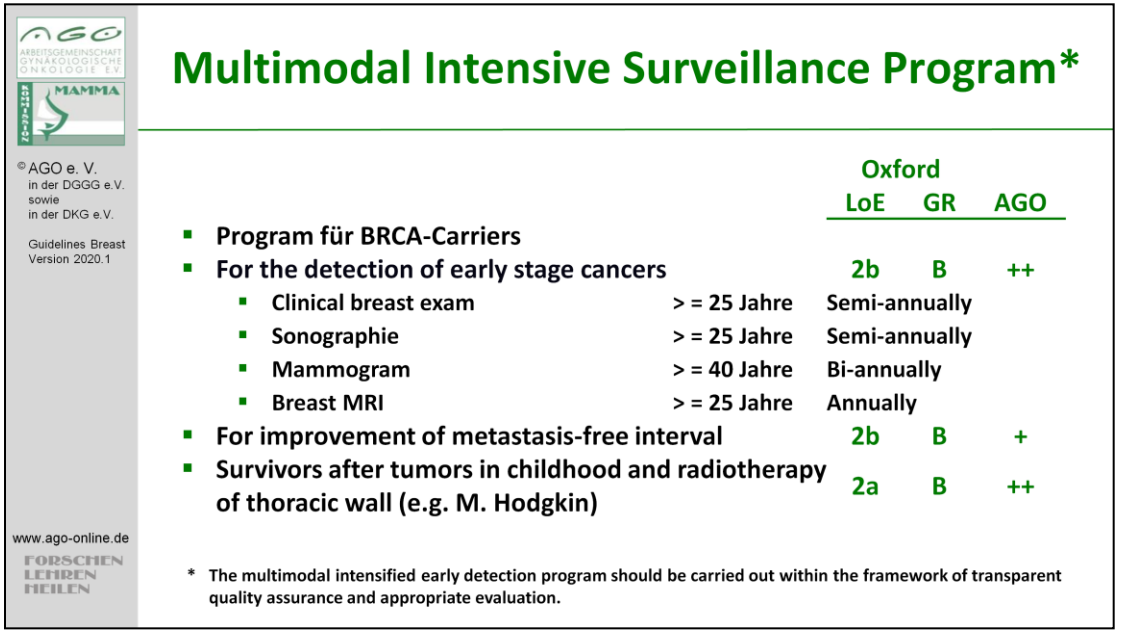

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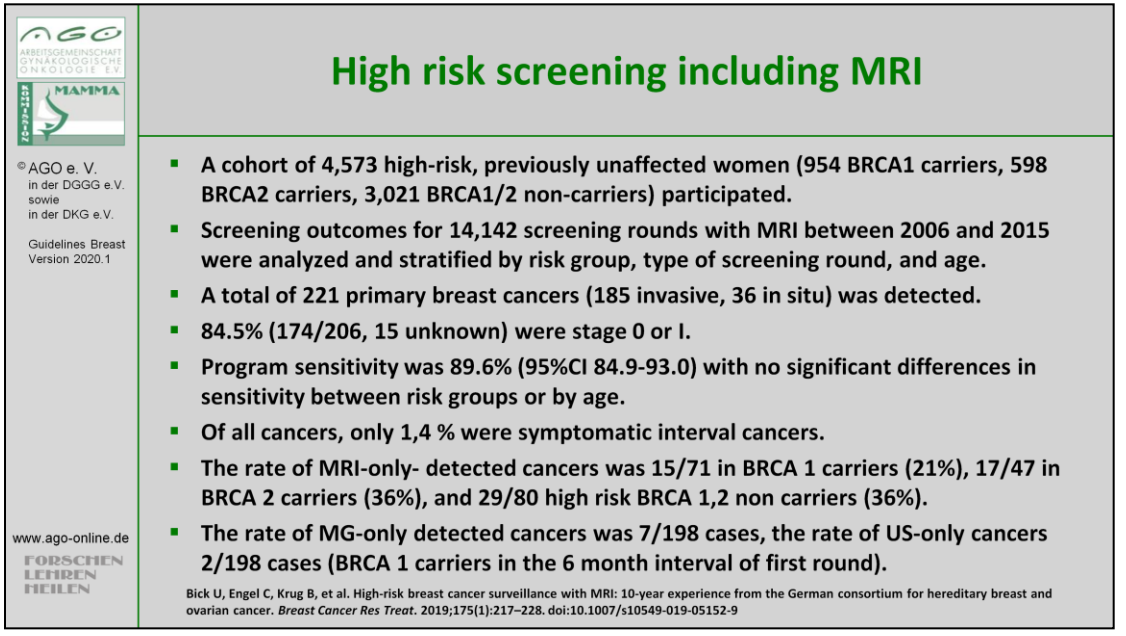

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High risk screening including MRI

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

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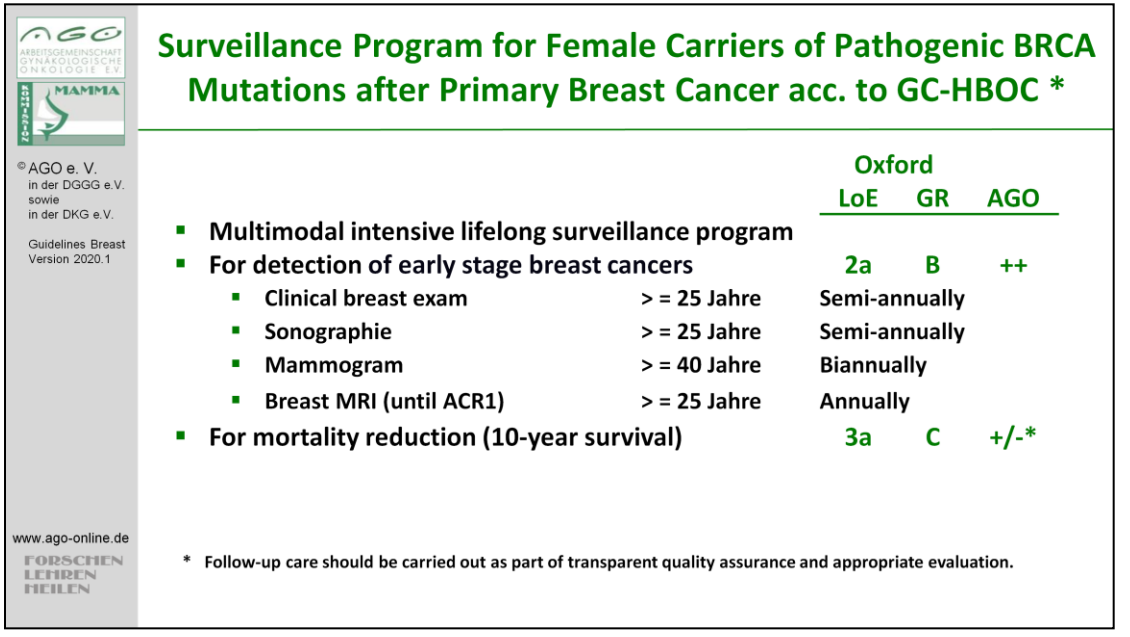

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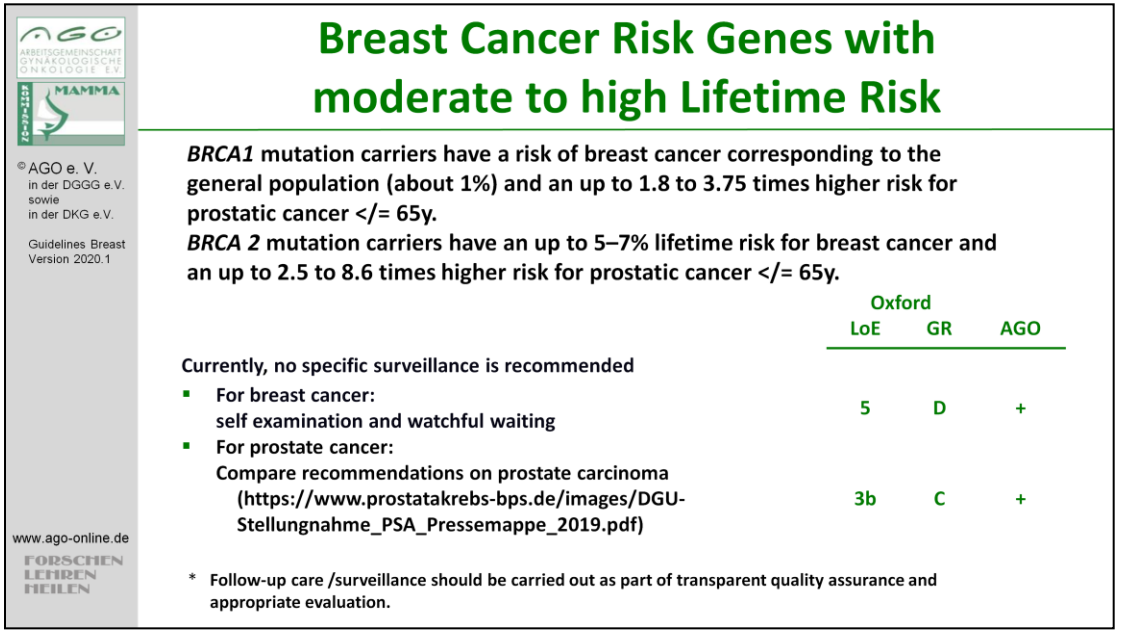

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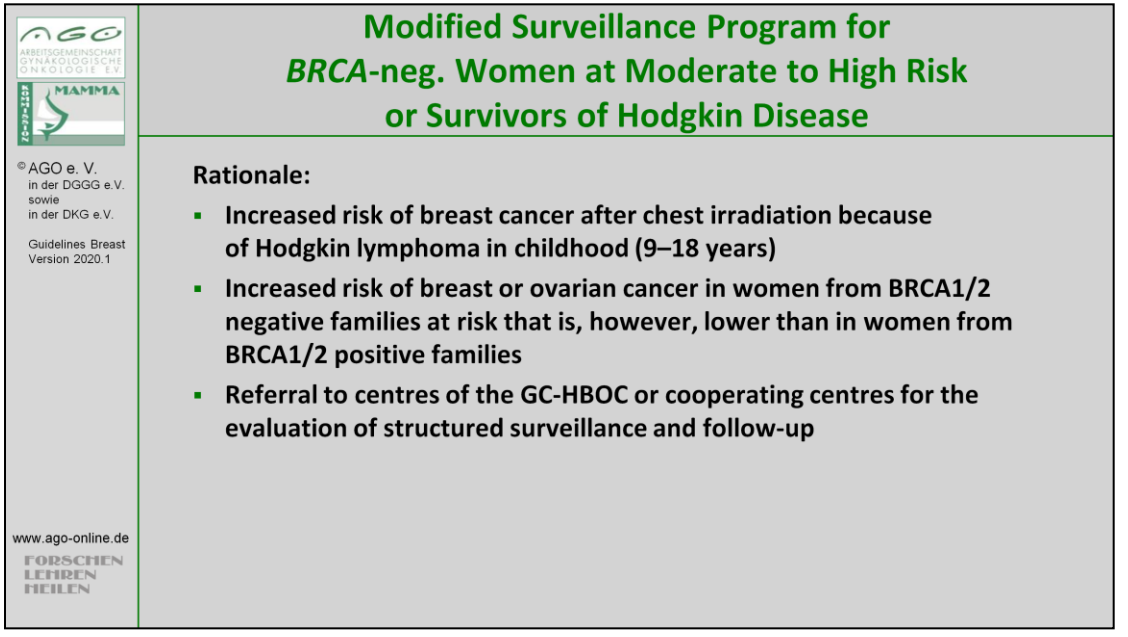

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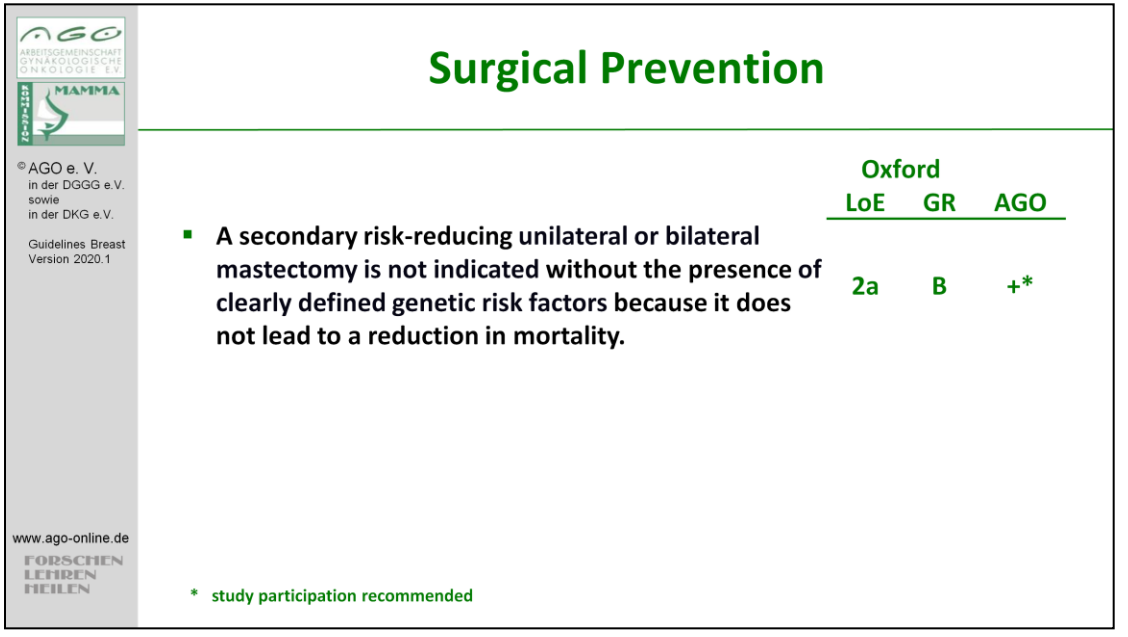
Schellong G[1], Riepenhausen M, German Consortium for Hereditary Breast and Ovarian Cancer et al.



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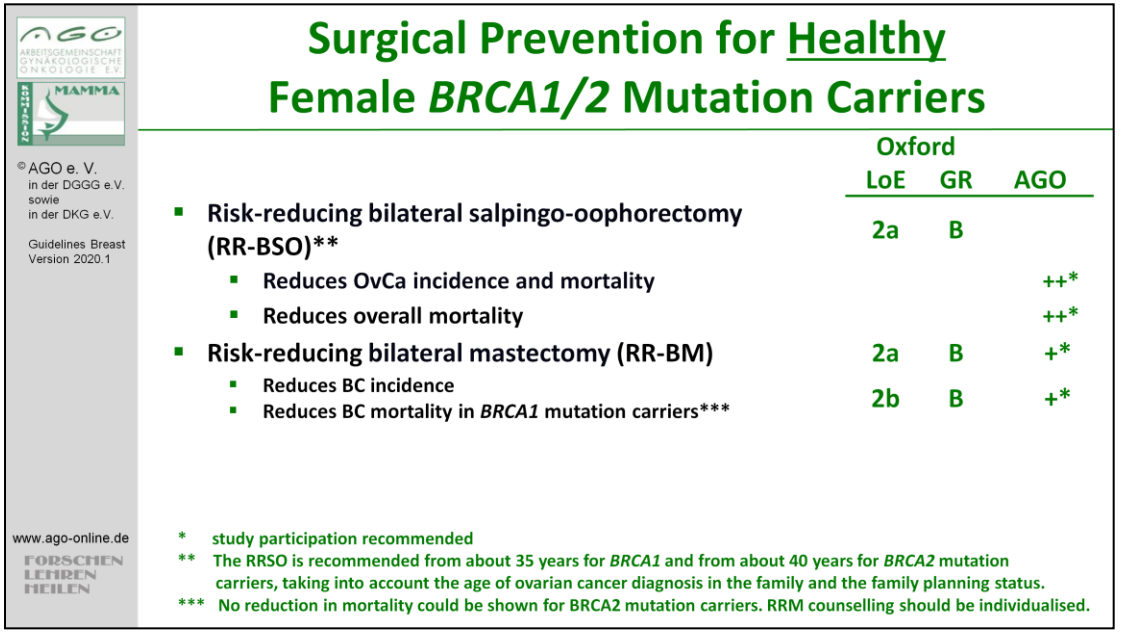

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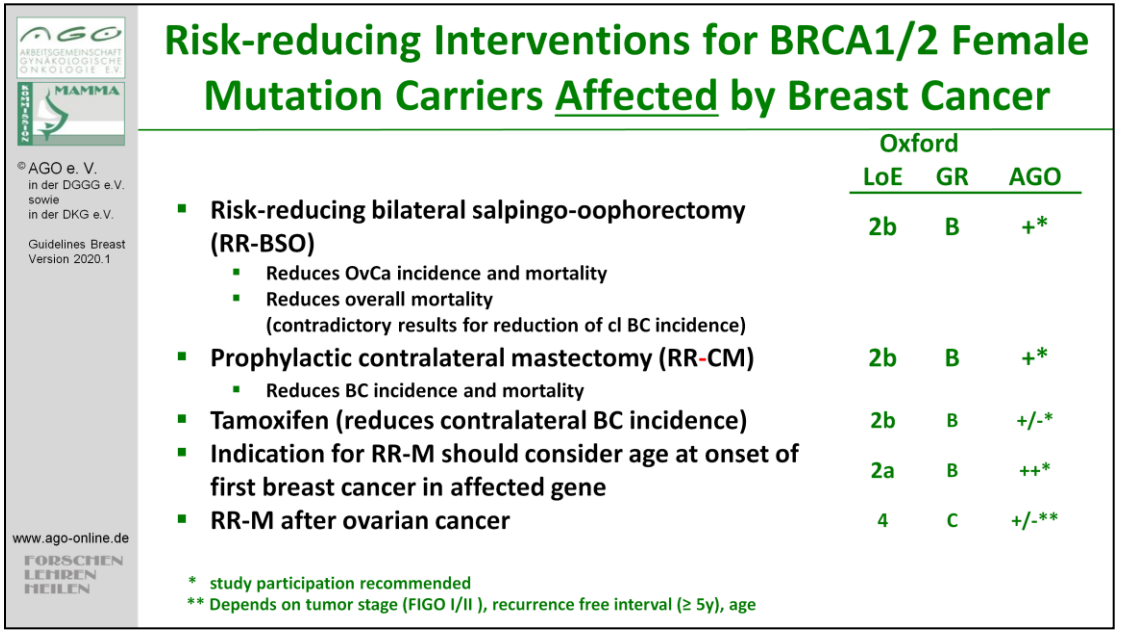

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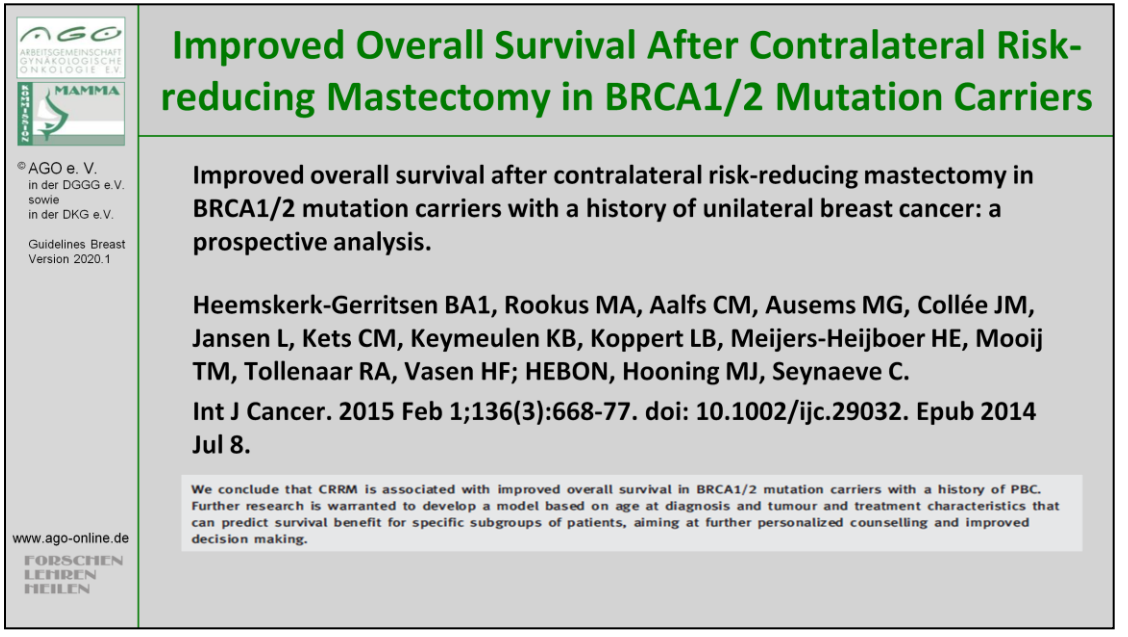

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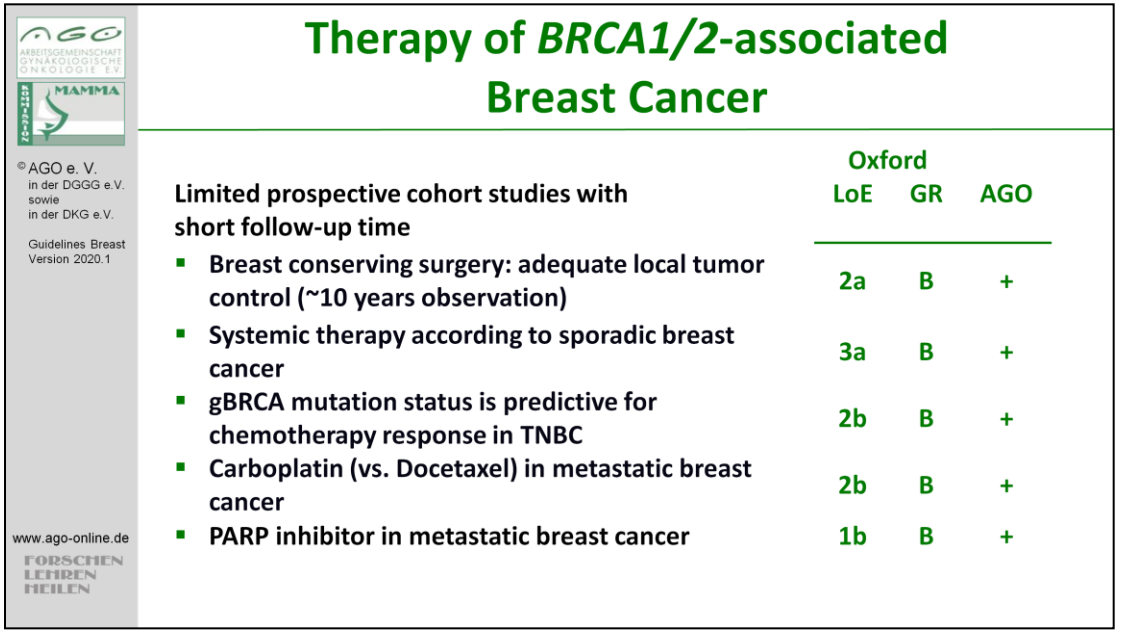

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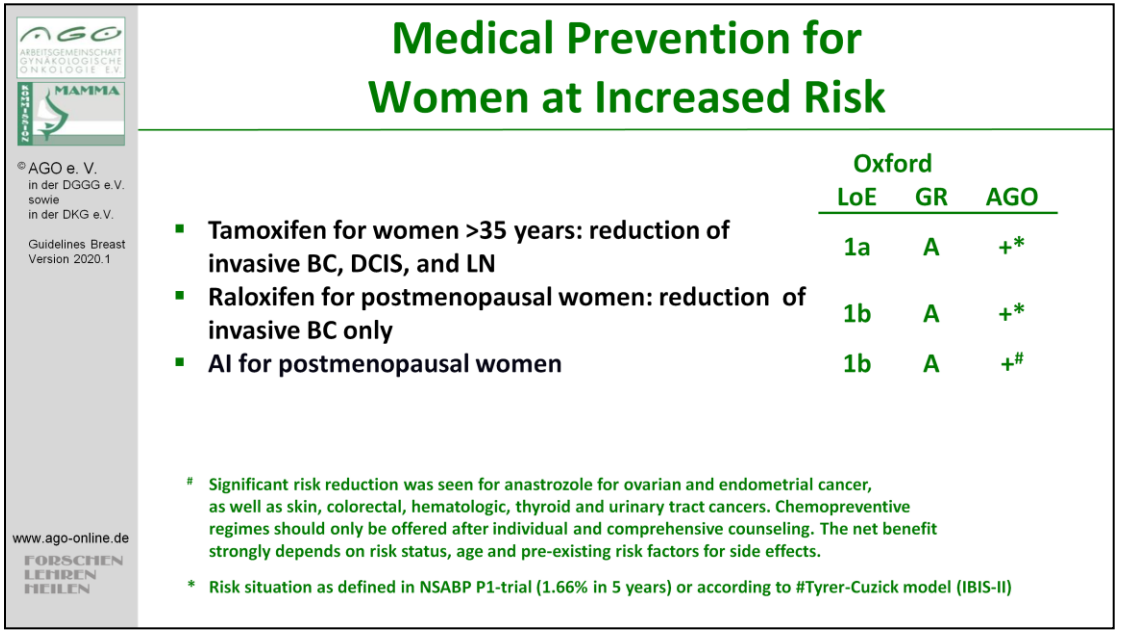

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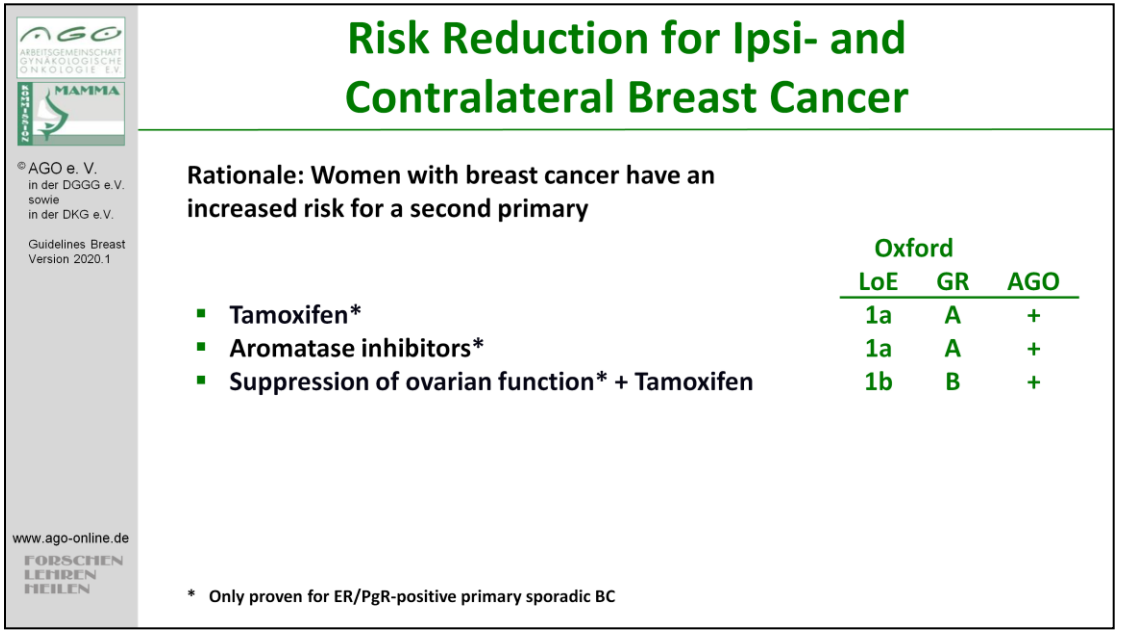

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Cooperation of Certified Breast Cancer (BC) Centres (Ctr) with Familial BC Ctr of the GC-HBOC*

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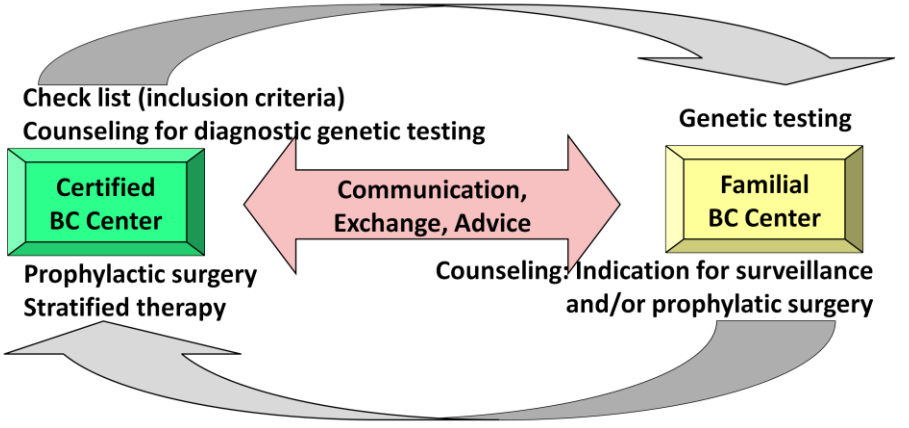

* trans-sectoral contract for integrated care, acc. to code of social law § 140a since 2015