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Cancer research
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Genetic susceptibility and management of hereditary breast cancer

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by SOLTI

Disclosures

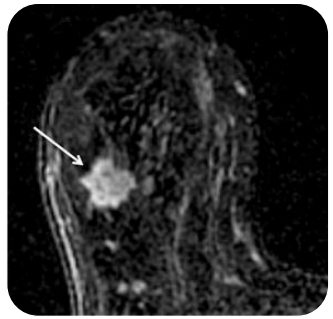
- Consultant for Pfizer and AstraZeneca

Estimation of cancer risk

- Identification of individuals at sufficient risk to consider enhanced screening or prevention strategies
- Reproductive decision making

Early detection and prevention

- Surveillance
- Risk reduction options

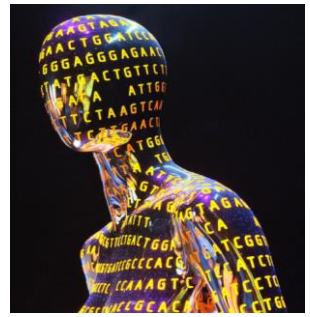


Targeted therapy

- Identification of tumours that might respond to targeted therapies

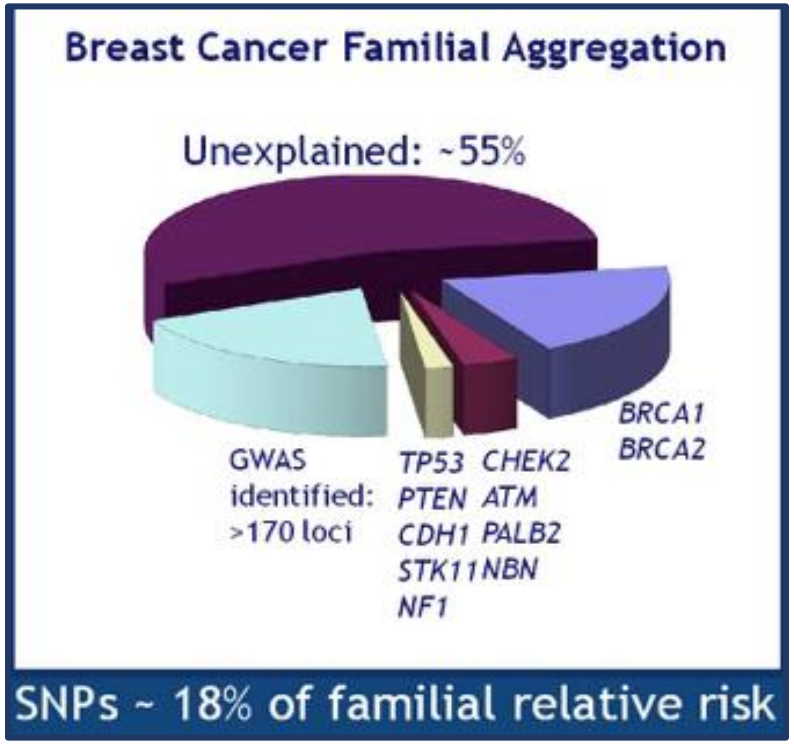
The changing paradigm of diagnostic testing for germline mutations in cancer genetics

Strong family history
Targeted testing
Genotype - phenotype
High penetrance



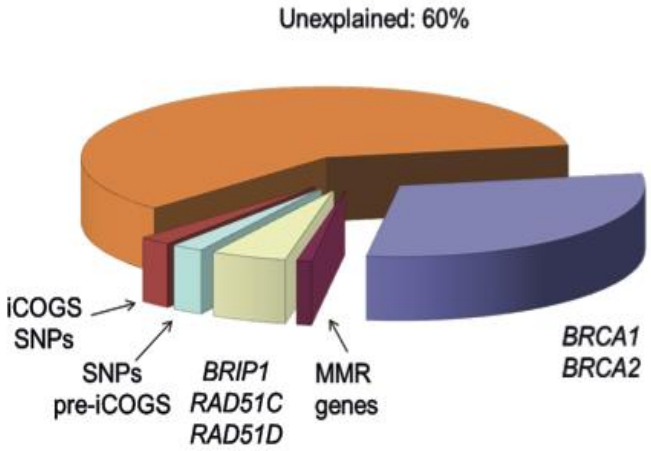
Panel and tumor testing
Weak/unknown correlations
Lower penetrance
Therapeutic implications and rapid turnover

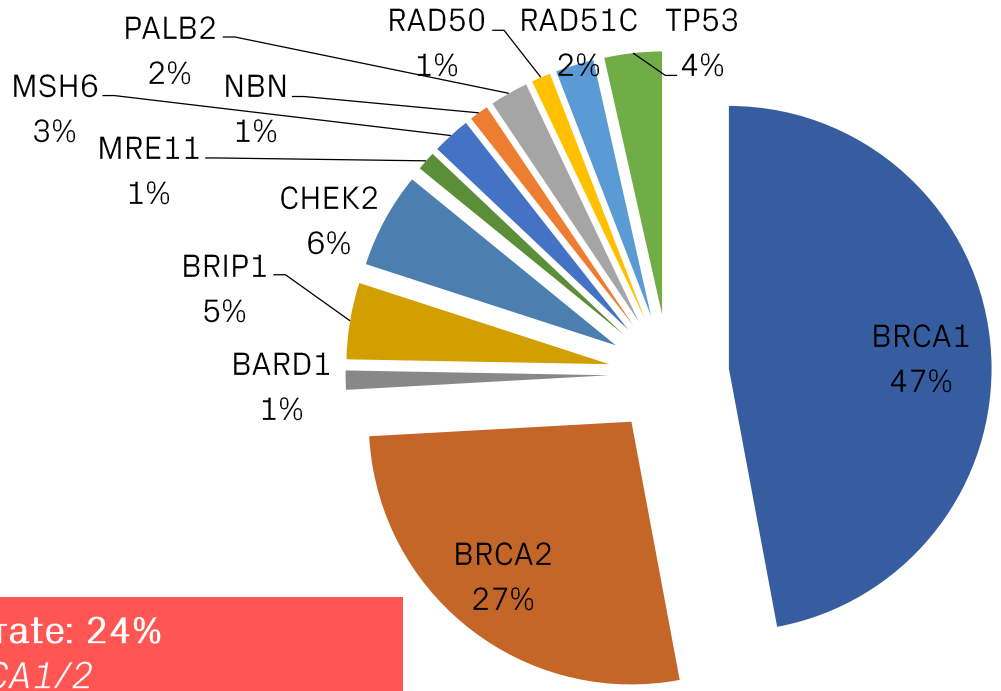
Susceptibility to breast cancer



Michailidou K, et al. Association analysis identifies 65 new breast cancer risk loci. Nature. 2017 Nov 2;551(7678):92-94.

Ovarian cancer genetic susceptibility

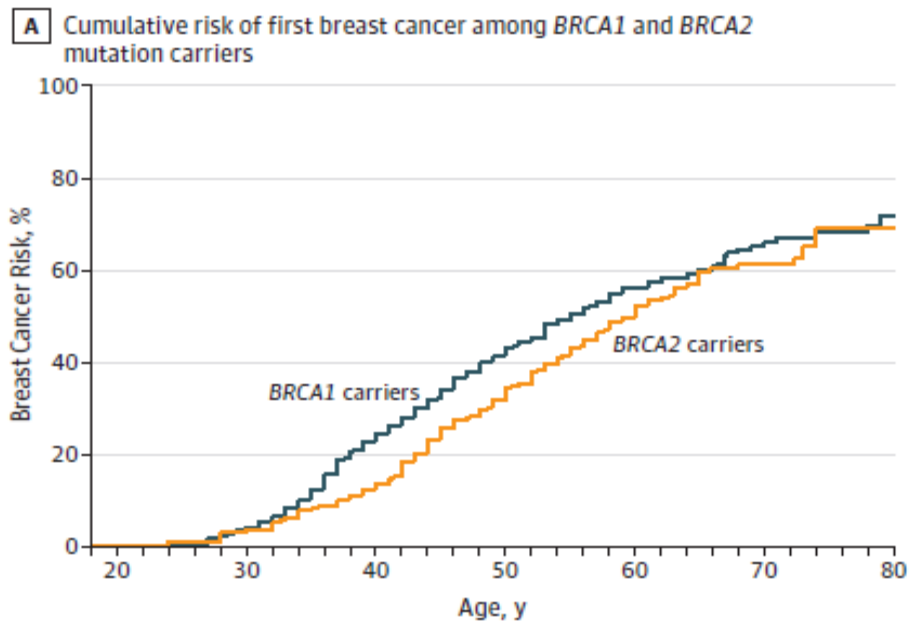


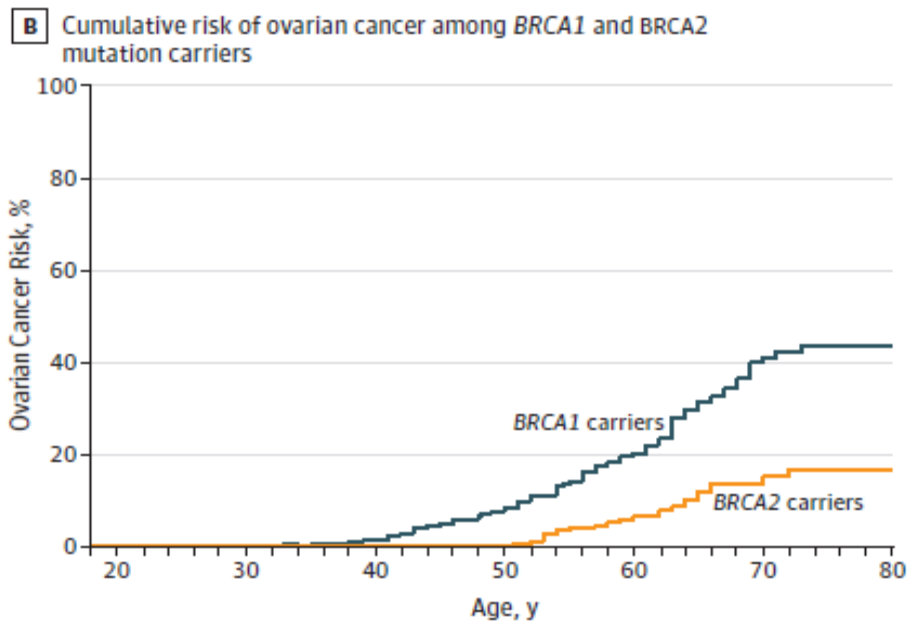


Mutation rate: 24%
- 18% *BRCA1/2*
- 6% Other genes

1. Kuchenbaecker KB, et al. Identification of six new susceptibility loci for invasive epithelial ovarian cancer. Nat Genet. 2015 Feb;47(2):164-71.
2. Walsh T, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci U S A. 2011 Nov 1;108(44):18032-7.

Estimated cumulative risk of breast and ovarian cancer in BRCA1/2 mutation carriers





Antoniou A, JAMA 2017.

Table 2. Associations between Pathogenic Variants in Established Breast Cancer–Predisposition Genes and Risk of Breast Cancer.*

Breast Cancer–Predisposition Gene[1,2,7]	Case Patients (N=32,247)	Controls (N=32,544)	Odds Ratio (95% CI)†	P Value
	no. with pathogenic variant (%)			
ATM	253 (0.78)	134 (0.41)	1.82 (1.46–2.27)	<0.001
BARD1	49 (0.15)	35 (0.11)	1.37 (0.87–2.16)	0.18
BRCA1	275 (0.85)	37 (0.11)	7.62 (5.33–11.27)	<0.001
BRCA2	417 (1.29)	78 (0.24)	5.23 (4.09–6.77)	<0.001
CDH1	17 (0.05)	6 (0.02)	2.50 (1.01–7.07)	0.06
CHEK2	349 (1.08)	138 (0.42)	2.47 (2.02–3.05)	<0.001
NF1‡	19 (0.06)	11 (0.03)	1.93 (0.91–4.31)	0.09
PALB2	148 (0.46)	38 (0.12)	3.83 (2.68–5.63)	<0.001
PTEN	8 (0.02)	3 (0.01)	NA	NA
RAD51C	41 (0.13)	35 (0.11)	1.20 (0.75–1.93)	0.44
RAD51D	26 (0.08)	14 (0.04)	1.72 (0.88–3.51)	0.12
TP53‡	19 (0.06)	2 (0.01)	NA	NA
Total	1621 (5.03)	531 (1.63)	—	—

BRCA1/2: 2.14% / 2.6%
ATM, CHEK2, PALB2, RAD51C, RAD51D: 2.53% / 2.77%

Table 1. Risk of Breast Cancer Overall Associated with Protein-Truncating Variants in 34 Genes in Population-Based Studies and All Studies.*

Gene	Population-Based Studies (48,826 patients and 50,703 controls)†				All Studies (60,466 patients and 53,461 controls)†	Prior Probability‡	BFDP
	No. of Carriers of Protein-Truncating Variants		Odds Ratio (95% CI)	P Value	P Value		
	Women with Breast Cancer	Controls					
ABRAXAS1	17	19	0.98 (0.50–1.94)	0.96	0.93	0.1	0.98
AKT1	3	6	0.47 (0.12–1.93)	0.29	0.14	0.1	0.94
ATM	294	150	2.10 (1.71–2.57)	9.2×10^{-13}	5.5×10^{-20}	0.8	1.3×10^{-18}
BABAM2	7	9	0.62 (0.23–1.71)	0.36	0.34	0.1	0.95
BARD1	62	32	2.09 (1.35–3.23)	0.00098	0.00011	0.2	0.0076
BRCA1	515	58	10.57 (8.02–13.93)	1.1×10^{-62}	3.7×10^{-65}	0.99	1.5×10^{-64}
BRCA2	754	135	5.85 (4.85–7.06)	2.2×10^{-75}	8.4×10^{-77}	0.99	3.1×10^{-76}
BRIP1	86	75	1.11 (0.80–1.53)	0.54	0.54	0.2	0.85
CDH1	11	12	0.86 (0.37–1.98)	0.72	0.58	0.2	0.94
CHEK2	704	315	2.54 (2.21–2.91)	3.1×10^{-39}	3.2×10^{-61}	0.99	1.3×10^{-60}
c.1100delC variant	548	245	2.66 (2.27–3.11)	1.1×10^{-33}	5.3×10^{-53}		
Other variants	156	70	2.13 (1.60–2.84)	3.0×10^{-7}	7.4×10^{-10}		
EPCAM	14	19	0.73 (0.36–1.49)	0.39	0.13	0.1	0.95
FANCC	71	65	1.26 (0.89–1.79)	0.20	0.20	0.1	0.87
FANCM	302	300	1.06 (0.90–1.26)	0.48	0.28	0.1	0.96
GEN1	31	43	0.66 (0.41–1.06)	0.088	0.18	0.1	0.95
MEN1	2	5	0.37 (0.07–1.97)	0.24	0.64	0.1	0.95
MLH1	5	9	0.58 (0.19–1.77)	0.34	0.55	0.1	0.95
MRE11	48	55	0.88 (0.59–1.32)	0.54	0.34	0.1	0.98
MSH2	13	13	1.06 (0.47–2.36)	0.89	0.80	0.1	0.92
MSH6	39	23	1.96 (1.15–3.33)	0.013	0.021	0.1	0.55
MUTYH	232	231	1.00 (0.83–1.21)	0.99	0.88	0.1	1.00
NBN	90	103	0.90 (0.67–1.20)	0.48	0.65	0.2	0.95
NF1	31	17	1.76 (0.96–3.21)	0.068	0.011	0.2	0.25
PALB2	274	55	5.02 (3.73–6.76)	1.6×10^{-26}	1.1×10^{-32}	0.99	2.9×10^{-32}
PIK3CA	3	12	0.21 (0.06–0.75)	0.016	0.19	0.1	0.94
PMS2	40	36	1.16 (0.73–1.85)	0.53	0.37	0.1	0.92
PTEN	14	6	2.25 (0.85–6.00)	0.10	0.0040	0.2	0.14
RAD50	120	121	1.08 (0.83–1.40)	0.57	0.45	0.1	0.95
RAD51C	54	26	1.93 (1.20–3.11)	0.0070	0.00026	0.3	0.0090
RAD51D	51	25	1.80 (1.11–2.93)	0.018	0.0018	0.3	0.044
RECQL	103	120	0.84 (0.64–1.10)	0.21	0.89	0.1	0.95
RINT1	32	49	0.72 (0.46–1.14)	0.17	0.31	0.1	0.96
STK11	6	5	1.60 (0.48–5.28)	0.44	0.50	0.2	0.70
TP53	7	2	3.06 (0.63–14.91)	0.17	0.015	0.8	0.033
XRCC2	15	18	0.96 (0.47–1.93)	0.90	0.81	0.1	0.98

1. Hu C, et al. A Population-Based Study of Genes Previously Implicated in Breast Cancer. N Engl J Med. 2021 Feb 4;384(5):440-451.
2. Breast Cancer Association Consortium, Dorling L, et al. Breast Cancer Risk Genes - Association Analysis in More than 113,000 Women. N Engl J Med. 2021 Feb 4;384(5):428-439.

Breast cancer susceptibility genes according to phenotype

	CARRIERS	BRIDGES
	OR	
	ER +	ER +
ATM	1,96 (1,52-2,53)	2,33 (1,87-1,92)
BARD1	0,91 (0,49-1,64)	1,40 (0,81-2,42)
BRCA1	3,39 (2,17-5,45)	3,92 (2,82-5,43)
BRCA2	4,66 (3,52-6,23)	5,69 (4,65-6,96)
CDH1	3,37 (1,24-10,72)	1,05 (0,42-2,63)
CHEK2	2,60 (2,05-3,31)	2,67 (2,30-3,11)
NF1	1,63 (0,65-4,03)	1,25 (0,61-2,55)
PALB2	3,13 (2,02-4,96)	4,45 (3,23-6,14)
PTEN	NA	2,42 (0,84-6,97)
RAD51C	0,83 (0,44-1,54)	1,31 (0,74-2,30)
RAD51D	1,61 (0,71-3,70)	1,52 (0,87-2,65)
TP53	NA	1,95 (0,32-11,82)

	CARRIERS	BRIDGES
	OR	
	TN	TN
ATM	0,50 (0,12-1,36)	0,91 (0,42-1,95)
BARD1	3,18 (1,16-7,42)	9,29 (4,58-18,85)
BRCA1	42,88 (26,56-71,25)	56,80 (41,18-78,34)
BRCA2	9,70 (5,97-15,47)	11,19 (8,27-15,16)
CDH1	NA	1,44 (0,18-11,28)
CHEK2	1,63 (0,7-3,20)	1,06 (0,63-1,76)
NF1	NA	2,02 (0,46-8,82)
PALB2	13,03 (7,08-23,75)	10,36 (6,42-16,71)
PTEN	NA	0 Cases
RAD51C	NA	5,71 (2,69-12,13)
RAD51D	NA	6,01 (2,73-13,24)
TP53	NA	0 Cases

1. Hu C, et al. A Population-Based Study of Genes Previously Implicated in Breast Cancer. N Engl J Med. 2021 Feb 4;384(5):440-451.
2. Breast Cancer Association Consortium, Dorling L, et al. Breast Cancer Risk Genes - Association Analysis in More than 113,000 Women. N Engl J Med. 2021 Feb 4;384(5):428-439.

Estimated absolute risk of breast cancer

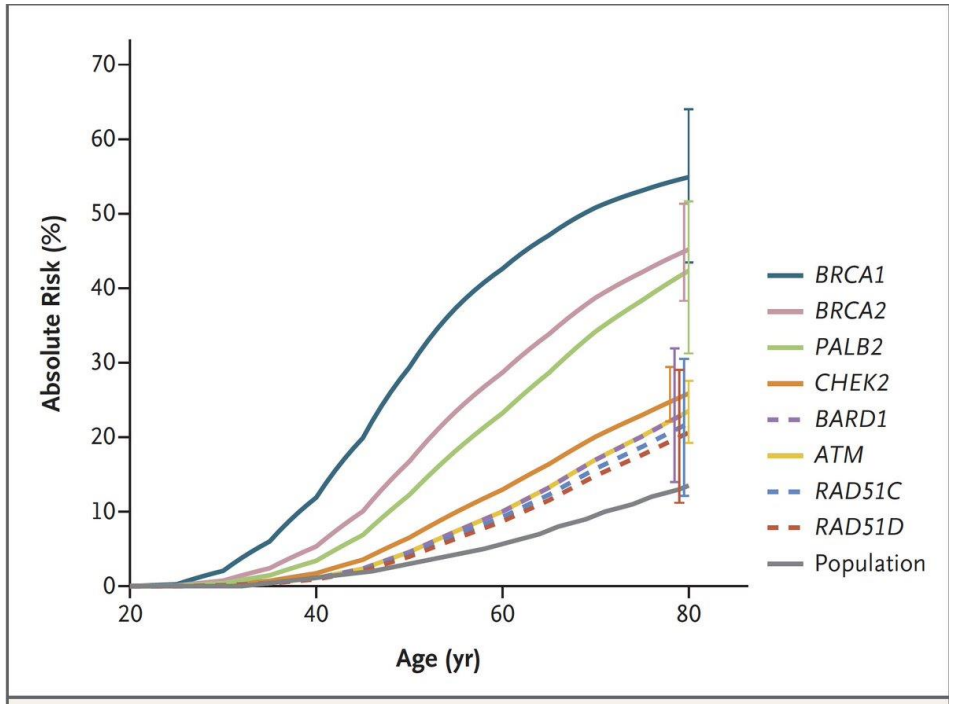


Figure 3. **Estimated Absolute Risk of Breast Cancer Associated with Protein-Truncating Variants in 8 Genes.**

Breast Cancer Association Consortium, Dorling L, et al. Breast Cancer Risk Genes - Association Analysis in More than 113,000 Women. N Engl J Med. 2021 Feb 4;384(5):428-439.

Polygenic risk score

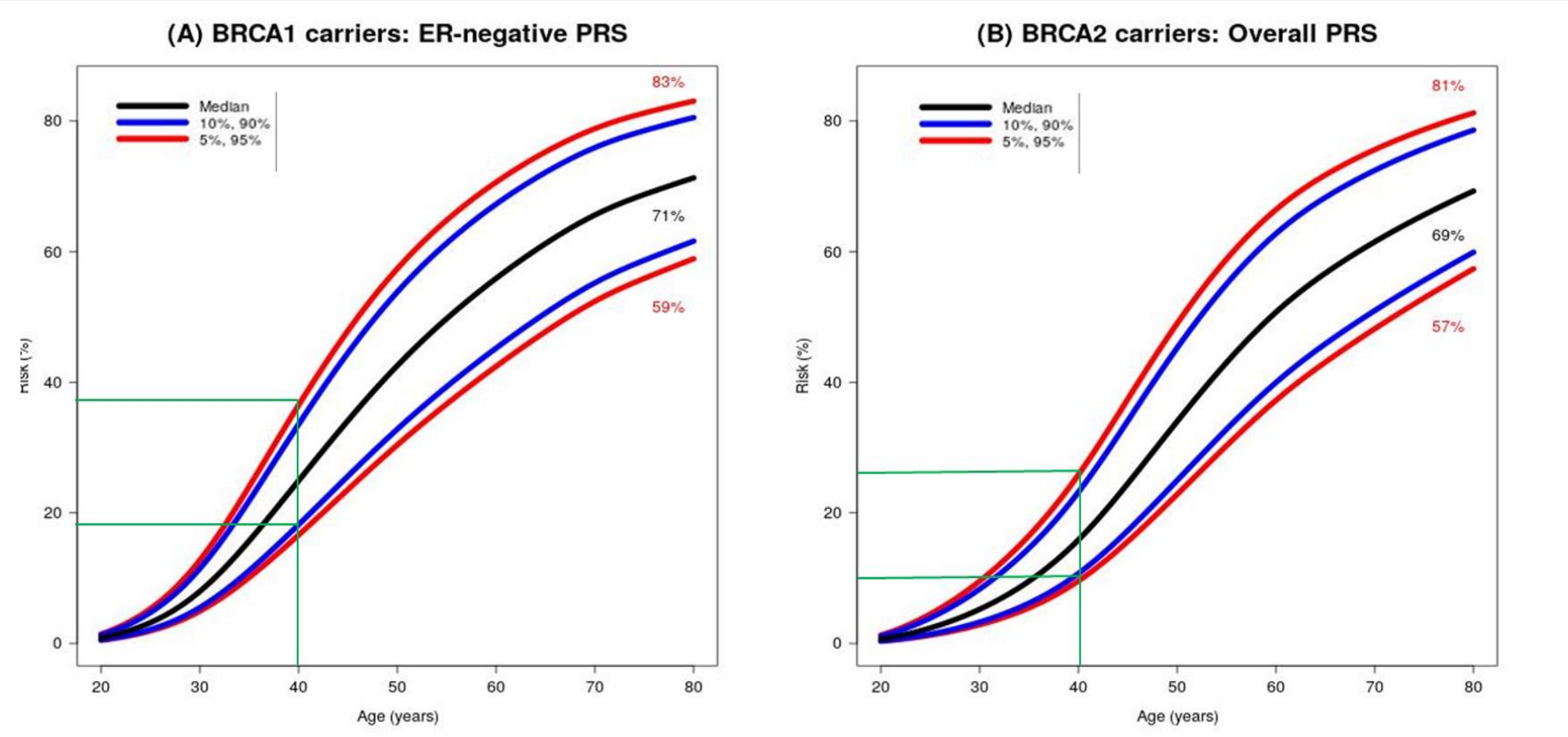
- Common genetic variants(SNPs)
- Low individual RR
- 313 SNPs associated to BC
- Combination of these SNPs may predispose or protect from BC de CM:

$$PRS_j = \sum_{i=1}^{313} n_{ij}\, ln(OR_i)$$

where n_{ij} is the number of risk alleles (0, 1, or 2) for variant i carried by individual j and OR_i is the per-allele OR for breast cancer associated with variant i. The ORs were obtained from the Breast Cancer Association Consortium (BCAC) study[11]

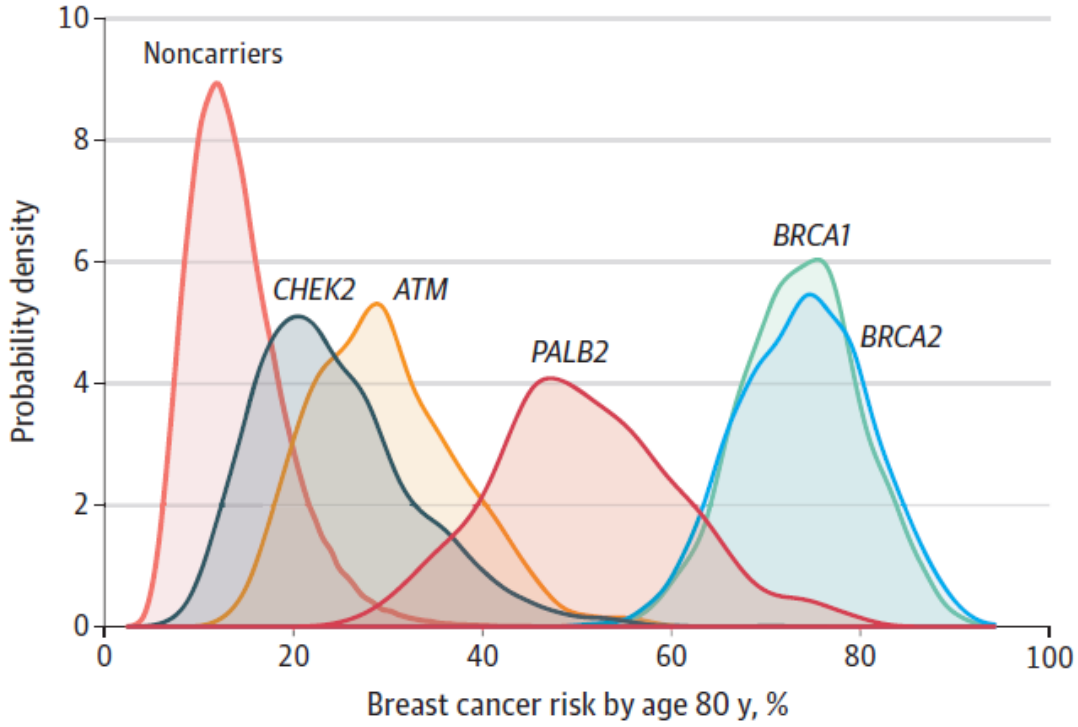
- Incorporated in some BC risk predictive models

PRS and breast cancer risks for BRCA1/2



Barnes DR, et al. Polygenic risk scores and breast and epithelial ovarian cancer risks for carriers of BRCA1 and BRCA2 pathogenic variants. Genet Med. 2020 Oct;22(10):1653-1666.

Modification of lifetime risk by PRS in noncarriers and mutation carriers



Gao C, et al. Risk of Breast Cancer Among Carriers of Pathogenic Variants in Breast Cancer Predisposition Genes Varies by Polygenic Risk Score. J Clin Oncol. 2021 Jun 8:JCO2001992.

Estimated lifetime risk by age 80 and modification according to PRS percentile, major gene and FH

TABLE 3. Lifetime Absolute BC Risk (by age 80 years) of BC for Different Pathogenic Variant Carriers With Respect to Different PRS Percentile and BC Family History Status

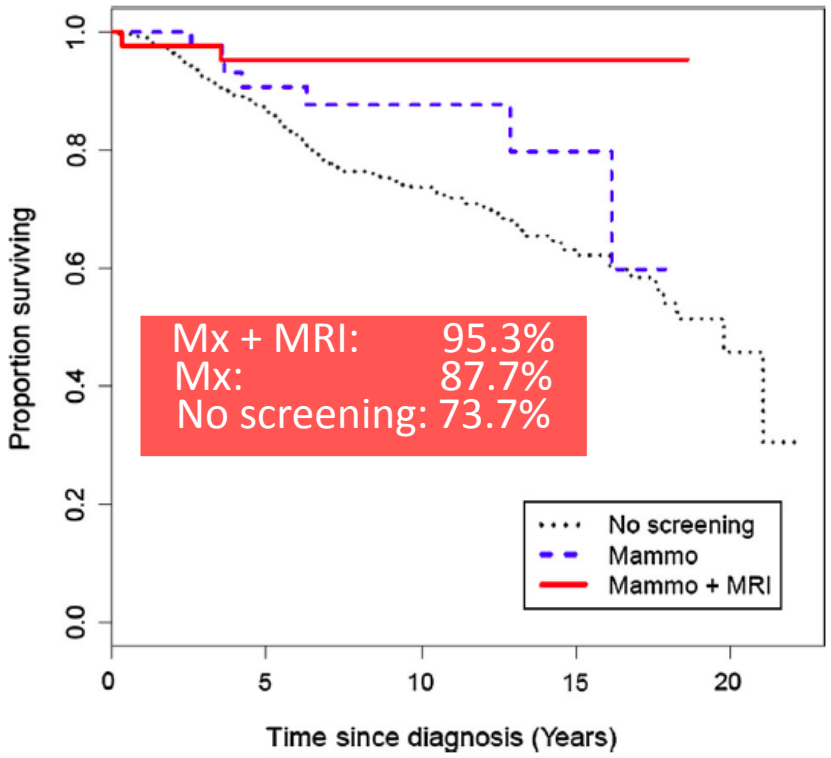
Lifetime Absolute Risk (95% CI)	No Family History				Family History of BC (First-Degree Relative)			
	10th Percentile PRS	Median PRS	Mean PRS	90th Percentile PRS	10th Percentile PRS	Median PRS	Mean PRS	90th% PRS
Noncarrier	6.7 (6.6 to 6.9)	11.1 (11.1 to 11.2)	12.1 (12.0 to 12.1)	18.3 (17.9 to 18.7)	9.1 (8.6 to 9.6)	14.8 (14.2 to 15.5)	15.9 (15.3 to 16.6)	23.9 (22.9 to 25.0)
BRCA1 carrier	36.1 (26.4 to 48.5)	41.2 (32.6 to 52.0)	41.4 (32.8 to 52.2)	46.9 (33.9 to 62.7)	45.4 (33.9 to 59.2)	51.1 (41.2 to 62.7)	51.3 (41.4 to 62.6)	57.3 (42.8 to 72.9)
BRCA2 carrier	43.8 (33.6 to 56.3)	49.3 (40.7 to 59.4)	49.5 (41.0 to 59.5)	55.3 (42.0 to 70.1)	53.9 (42.4 to 66.9)	59.8 (50.7 to 69.9)	59.9 (50.8 to 69.8)	65.9 (51.8 to 79.3)
ATM carrier	12.8 (10.3 to 15.9)	20.5 (16.7 to 25.2)	21.9 (18.0 to 26.6)	32.3 (26.8 to 38.8)	17.0 (13.7 to 21.1)	26.7 (21.9 to 32.5)	28.2 (23.3 to 34.0)	40.9 (34.2 to 48.5)
CHEK2 carrier	15.2 (12.6 to 18.2)	24.1 (20.3 to 28.5)	25.5 (21.6 to 30.0)	37.3 (32.0 to 43.4)	20.0 (16.7 to 24.0)	31.1 (26.3 to 36.6)	32.6 (27.8 to 38.0)	46.6 (40.3 to 53.4)
PALB2 carrier	21.5 (15.4 to 29.7)	33.2 (24.2 to 44.2)	34.6 (25.7 to 45.3)	49.2 (37.6 to 62.1)	27.9 (20.1 to 38.0)	41.9 (31.3 to 54.3)	43.1 (32.7 to 54.7)	59.5 (46.8 to 72.0)

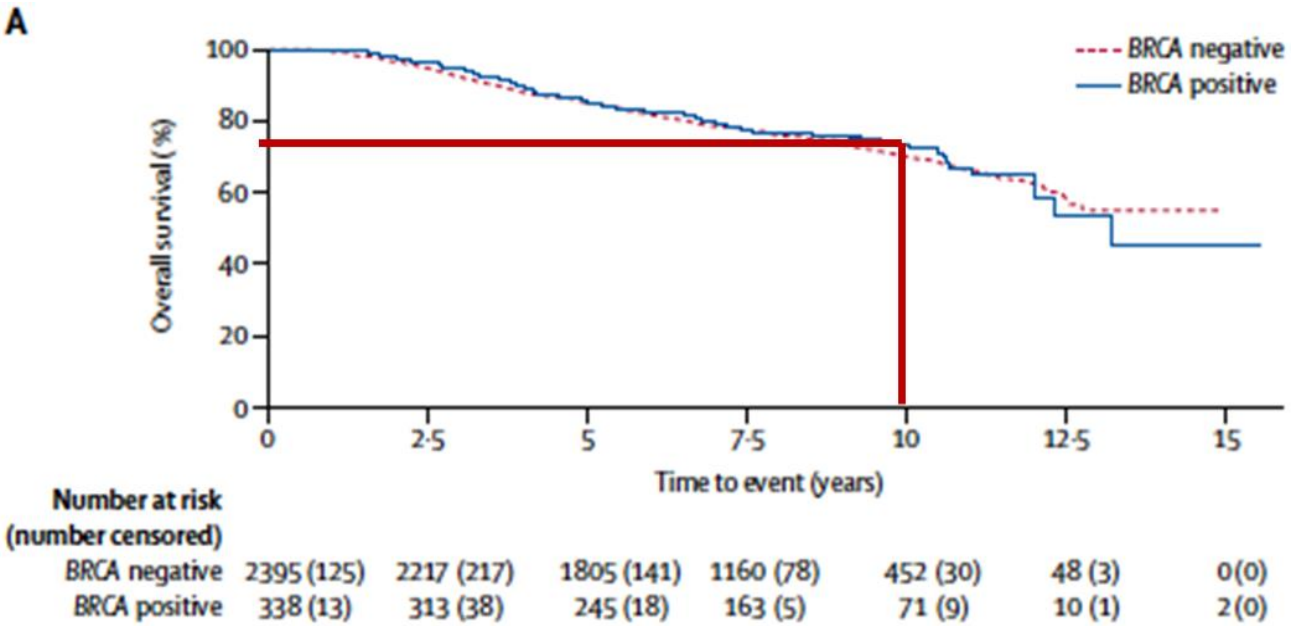
Gao C, et al. Risk of Breast Cancer Among Carriers of Pathogenic Variants in Breast Cancer Predisposition Genes Varies by Polygenic Risk Score. J Clin Oncol. 2021 Jun 8:JCO2001992.

Performance of MRI for BC screening in high risk women

Study	N	Sensitivity	Specificity	LN -	≤ 10 mm	Interval	MRI+/Mx-
Kriege et al, NEJM 2004	1909	80 %	90%	79%	43%	8%	49% T/ 1% ♀
Warner et. al., JAMA 2004	236	77%	95%	86%	56%	5%	32% T/ 3% ♀
MARIBS Study group, Lancet 2005	649	77%	81%	80%	44%	6%	54% T/ 3%♀
Kuhl et. al., JCO 2005	529	91%	97%	84%	38%	2%	44% T/ 4% ♀
Kuhl et. al., JCO 2010	687	93%	98%	89%	77%	0	52% T/ 2% ♀
Sardanelli et. al. Invest Radiol 2011	501	91%	97%	72%	48%	6%	31% T/ 3% ♀
Riedl et. al., JCO 2015	559	90 %	89 %	90%	67.5%	3%	45% T/ 5% ♀
Sung et. al., Radiology 2016	7519	75%	NR	NR	NR	5%	80%T/ 1% ♀
Lo et. al., Radiology 2017	1249	96%	93.7%	82%	46%	0	64%T/ 2%♀
Vreeman et. al. Radiology 2018	2463	81%	95.1 %	80%	NR	11%	32%T / 2%♀

Survival impact of MRI-based BC screening in high risk women





1. Evans DG, et al, Howell A, Duffy SW. MRI breast screening in high-risk women: cancer detection and survival analysis. Breast Cancer Res Treat. 2014 Jun;145(3):663-72. doi: 10.1007/s10549-014-2931-9. Epub 2014 Apr 1.

2. Copson ER, et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. Lancet Oncol. 2018 Feb;19(2):169-180. doi: 10.1016/S1470-2045(17)30891-4. Epub 2018 Jan 11. PMID: 29337092; PMCID: PMC5805863.

Is mammography still needed?

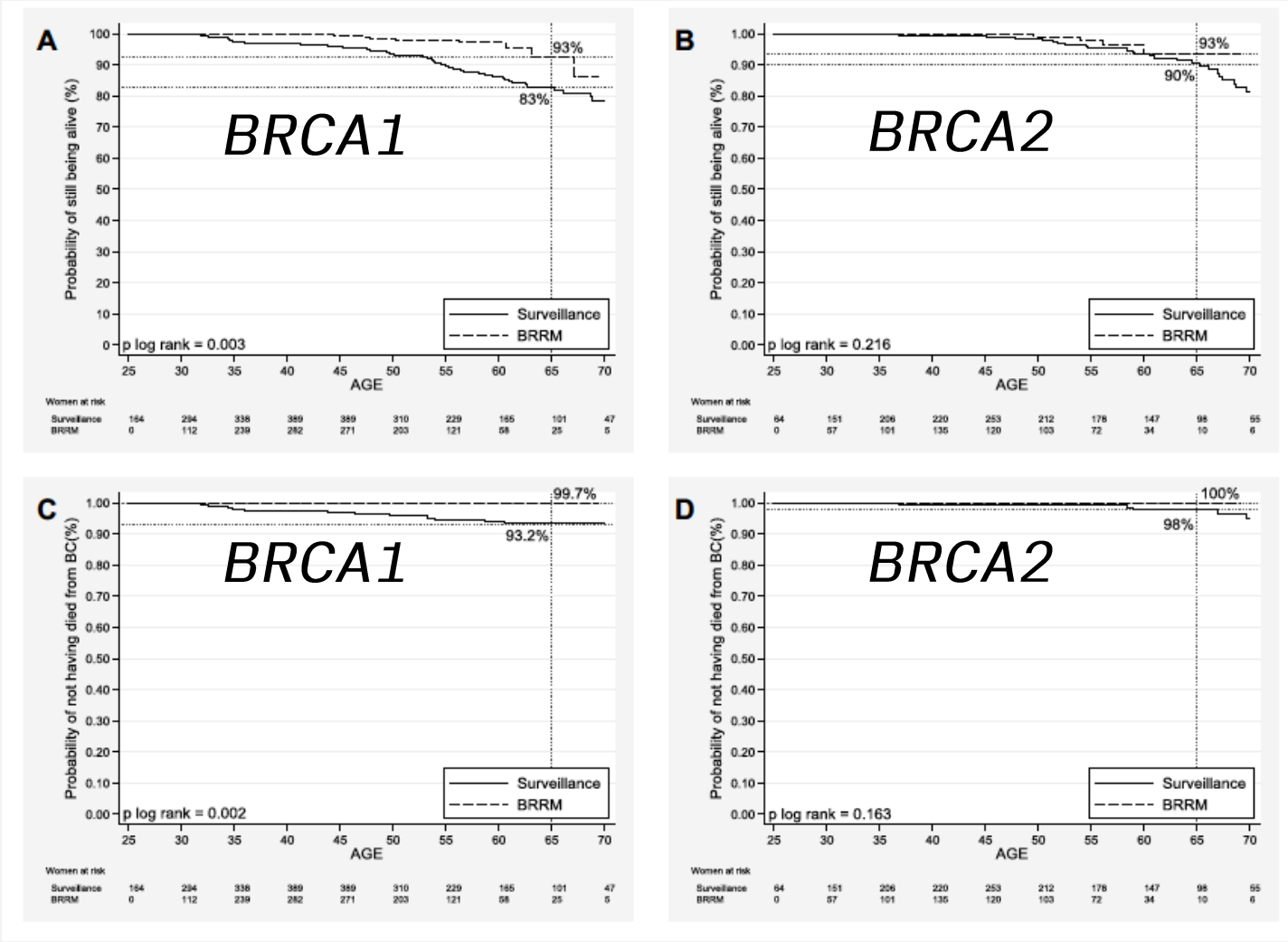
Pub.	Study	BC	Only seen on Mx	Type of tm
Warner, 2004		22	2	2 DCIS
Leach, 2005	MARIBS	20	2	2 DCIS
Kuhl, 2005		43	1	1 DCIS
Rijnsburger,2010	MRISC	47	5	3 DCIS
Kuhl, 2010	EVA	27	2	1 DCIS
Sardanelli, 2011	HIBCRIT-1	52	1	1 ILC
Obdeijn, 2014		94	2	2 DCIS
Riedl, 2015		40	2	2 DCIS with microinvasion
Vreeman, 2018		170	11	7 DCIS
Bick, 2019		221	5	4 DCIS
Total		**736**	**33 (4.5%)**	**22 (66%) DCIS**

Performance of MRI plus Mx in the High risk Ontario Breast Screening program

- Prospective cohort study 8782 high-risk women age 30-69 years
- MRI and Mx combined compared with each modality individually
- **Mut carriers age 30-39 years:**
  - MRI + Mx: similar sensitivity to MRI alone (100% vs. 97%), but decreased specificity (78% vs 86%)
- **Women age 50-69 years:**
  - MRI + Mx: increased sensitivity compared with MRI alone (96% vs. 915)

Chiarelli AM, et al. Performance Measures of Magnetic Resonance Imaging Plus Mammography in the High Risk Ontario Breast Screening Program. J Natl Cancer Inst. 2020 Feb 1;112(2):136-144.

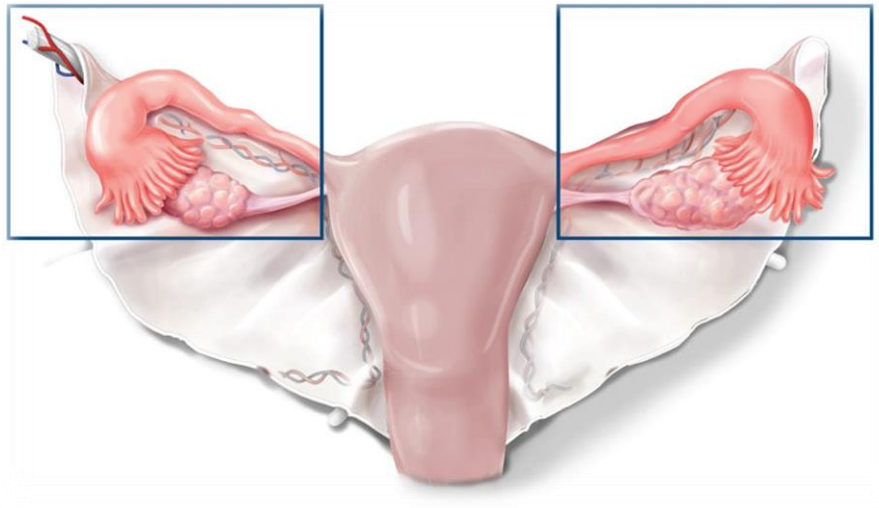
Impact of BRRM in healthy BRCA mutation carriers



Heemskerk-Gerritsen BAM, et al. Survival after bilateral risk-reducing mastectomy in healthy BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat. 2019 Oct;177(3):723-733.

Prophylactic salpingoophorectomy

- Bilateral salpingo-oophorectomy (BSO) reduces the risk of ovarian, Fallopian tube and primary peritoneal cancer by 80-95%



MORTALITY	HR	95% CI
All-cause	0.40	0.26-0.61
Ovarian cancer-specific	0.21	0.06-0.80

PBSO and BC risk reduction

		Mavvaddat, 2013	Heemskerk, 2016	Domchek, 2016	Kauff, 2016	Kotsopoulos, 2017
	Study	EMBRACE	HEBON	PROSE re-analysis	Kauff re-analysis	HBCCSG
	BRCA1/BRCA2	501/485 (51%/49%)	589/233 (72%/28%)	970/597 (62%/38%)	220/125 (64%/36%)	2969/725 (80%/20%)
BRCA1	BRCA1	(BC/pts)	(BC/PYO)	(BC/pts)	(BC/pts)	(BC/PYO)
	With RRSO	9/162	36/1238	40/294	6/100	122/6055
	Without RRSO	26/339	39/1609	137/676	11/120	170/10806
	HR (95% CI)	0.52 (0.24-1.13)	1.21 (0.72-2.06)	0.63 (0.42-0.93)	0.47 (0.16-1.37)	0.96 (0.73-1.26)
BRCA2	BRCA2	(BC/pts)	(BC/PYO)	(BC/pts)	(BC/pts)	(BC/PYO)
	With RRSO	9/146	6/400	13/155	2/60	21/2163
	Without RRSO	20/339	8/580	96/442	5/65	36/1550
	HR (95% CI)	0.79 (0.35-1.8)	0.54 (0.17-1.66)	0.40 (0.19-0.84)	0.47 (0.06-3.86)	0.65 (0.37-1.16)

Premenopausal PBSO and breast cancer risk reduction

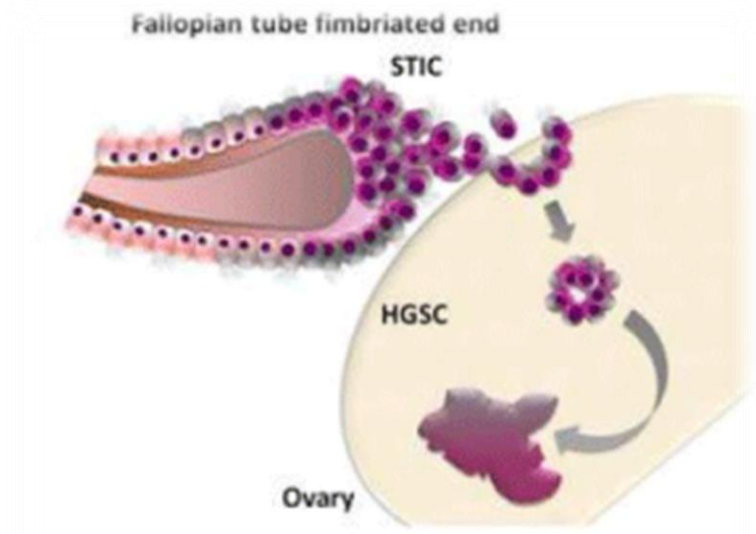
		Mavvaddat, 2013	Kotsopoulos, 2016	Stjepanovic, 2020
	Study	EMBRACE	HBCCSG	RiCO
		RRSO <45y	RRSO <50y BC < 50y	RRSO<51y
BRCA1	BRCA1	(BC/pts)	(BC/PYO)	(BC/PYO)
	With RRSO	4/97	54/2708	11/567
	Without RRSO	26/339	140/9594	43/1150
	HR (95% CI)	0.38 (0.13-1.13)	0.79 (0.55-1.13)	0.45 (0.22-0.92)
BRCA2	BRCA2	(BC/pts)	(BC/PYO)	(BC/PYO)
	With RRSO	4/76	3/571	11/438
	Without RRSO	20/339	27/1585	31/1134
	HR (95% CI)	0.44 (0.14-1.38)	0.18 (0.05-0.63)	0.77 (0.35-1.67)

Impact of RRBSO on QOL, menopausal symptoms and sexual function

- Fewer breast and ovarian cancer worries compared to surveillance
- No adverse impact on generic QOL of high-risk women, but impacts on menopause-specific QOL:
  - More endocrine symptoms and worse sexual functioning (54%)
- These symptoms are improved by HRT, but not to pre-surgical levels
- Nevertheless, satisfaction with the decision to undergo RRSO remains high (1 year).

Madalinska, JCO 2005; Finch, Gynecol Oncol 2011; Finch, Psychooncology 2013; Vermeulen, BRCA congress Montreal 2016

Salpingectomy with delayed RRSO vs. RRSO

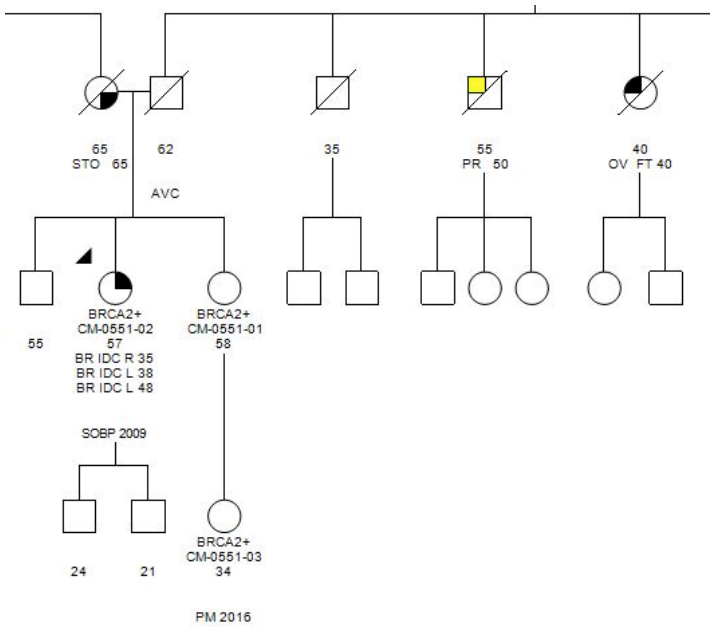


Fallopian tube: STICS

JUBA study

- 577 women, 394 underwent RRS and 154 underwent RRSO
- Mean age:
  - RRS: 35 and 38 y (BRCA1)
  - RRSO: 37 and 41y (BRCA2)
- No cases of ovarian or peritoneal cancer during follow-up
- RRS vs RRSO:
  - Better menopause-related QoL, regardless of HRT
  - Better sexual functioning, regardless of HRT
  - Similar decline in cancer worry
  - No significant differences in Health-related QoL, decisional conflict, decisional regret, or surgical outcomes

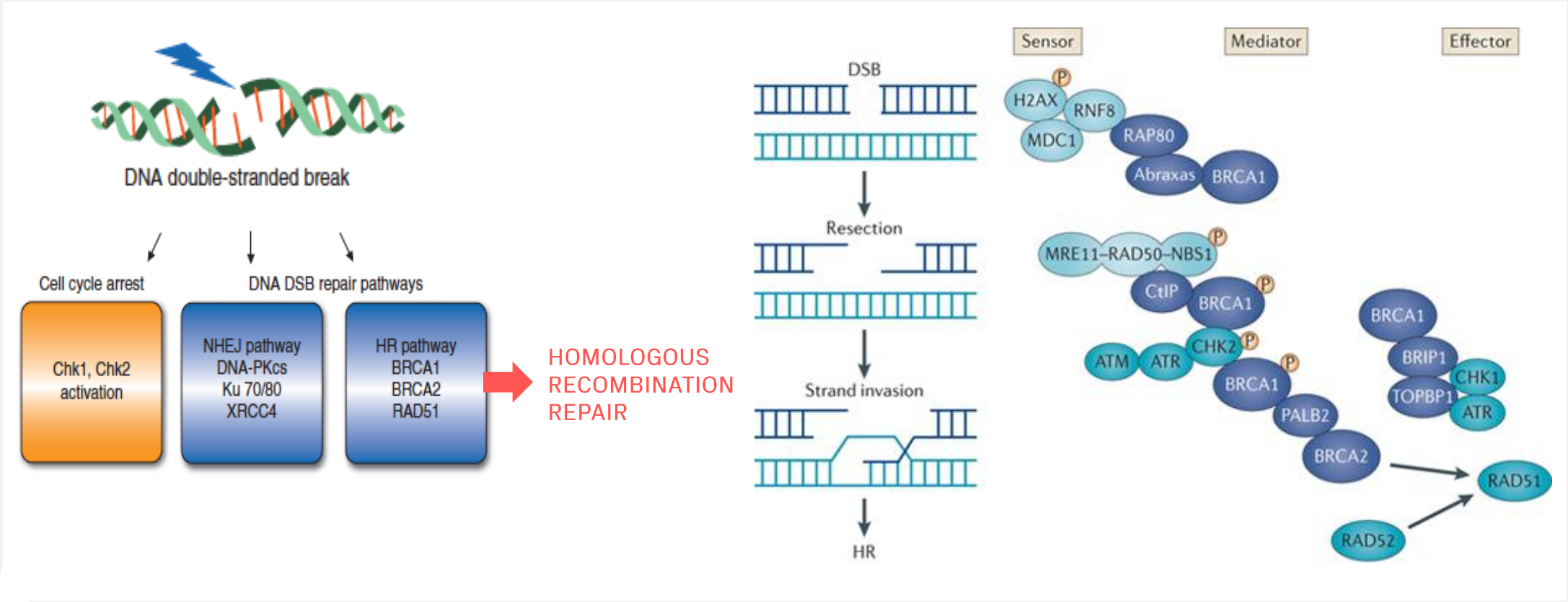
Steenbeek MP, et al. Association of Salpingectomy With Delayed Oophorectomy Versus Salpingo-oophorectomy With Quality of Life in BRCA1/2 Pathogenic Variant Carriers: A Nonrandomized Controlled Trial. JAMA Oncol. 2021 Jun 3:e211590.



39% and **20%** of *BRCA1/2* mutation carriers and partners would consider preimplantation genetic diagnosis or prenatal diagnosis, respectively

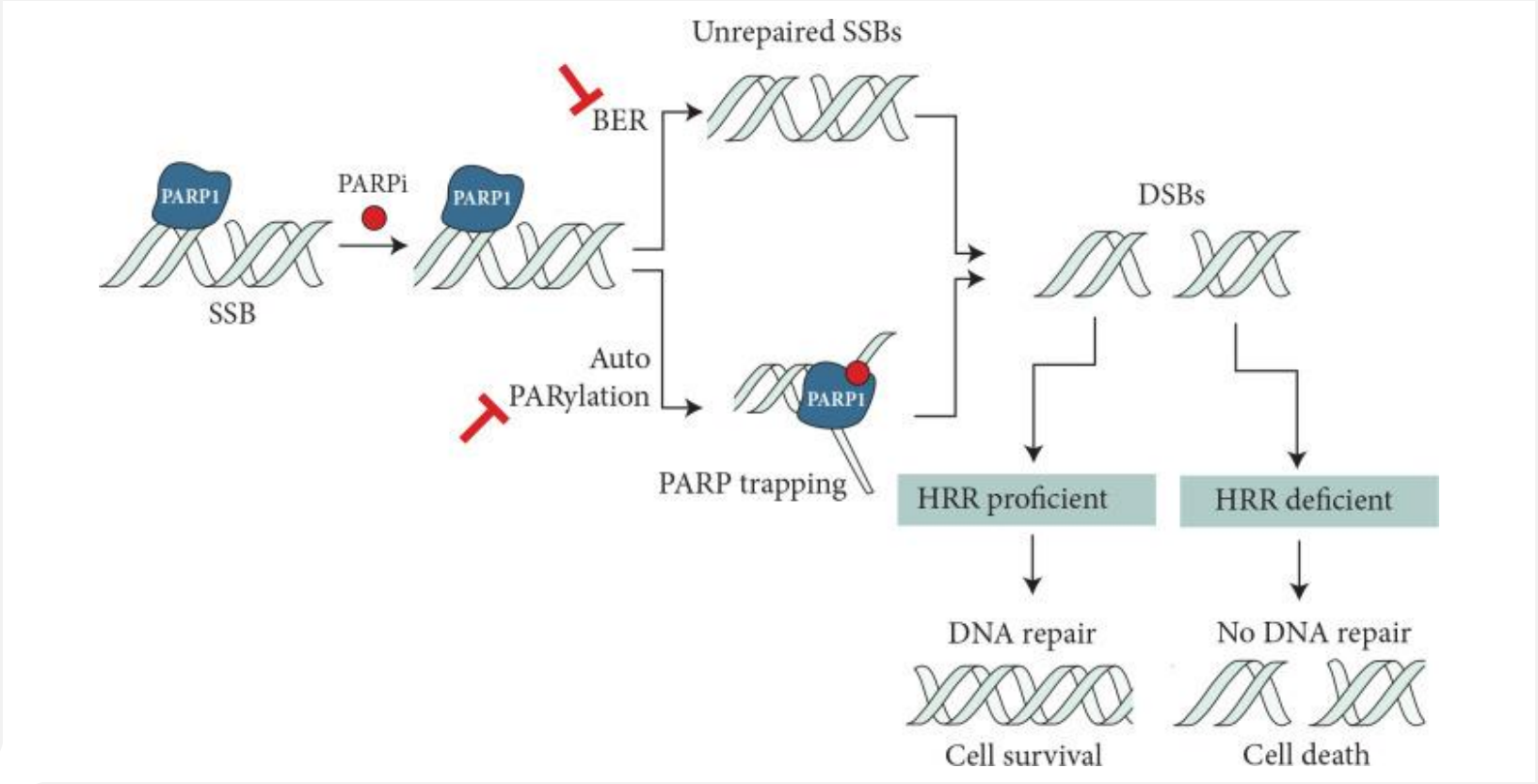
Gietel-Habets J, et al. Awareness and attitude regarding reproductive options of persons carrying a BRCA mutation and their partners. Hum Reprod. 2017 Mar 1;32(3):588-597.

BRCA1 and BRCA2 are essential proteins for DNA repair by homologous recombination



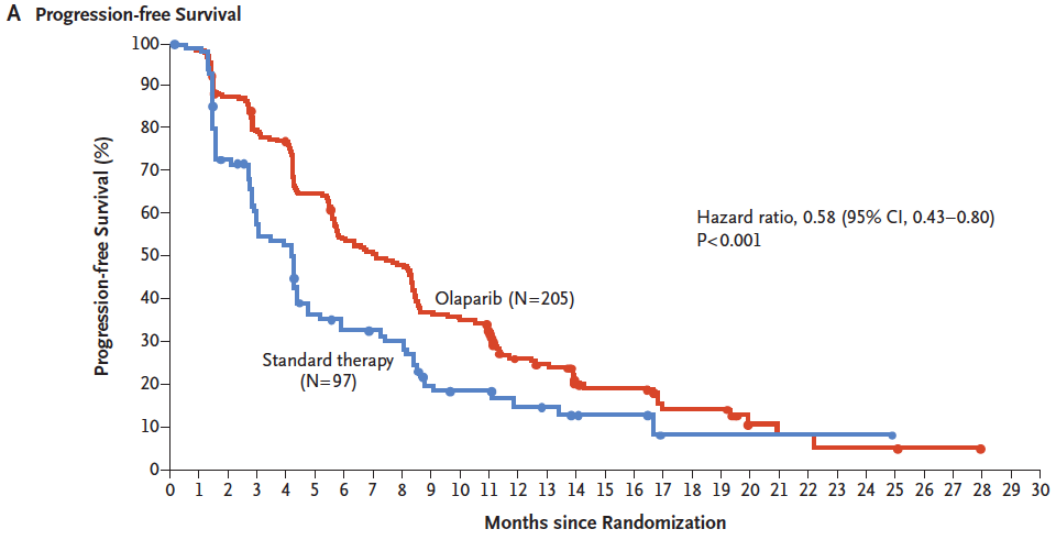
1. Roy R, Chun J, Powell SN. BRCA1 and BRCA2: different roles in a common pathway of genome protection. Nat Rev Cancer. 2011 Dec 23;12(1):68-78.
2. Lee JM, Ledermann JA, Kohn EC. PARP Inhibitors for BRCA1/2 mutation-associated and BRCA-like malignancies. Ann Oncol. 2014 Jan;25(1):32-40.

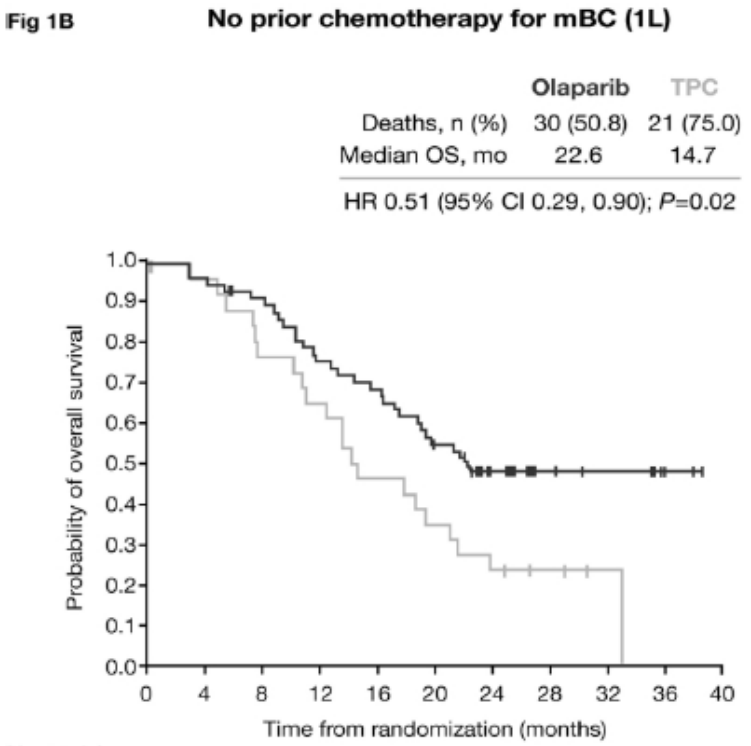
Mechanism of action of PARPi



Mateo J, et al. A decade of clinical development of PARP inhibitors in perspective. Ann Oncol. 2019 Sep 1;30(9):1437-1447.

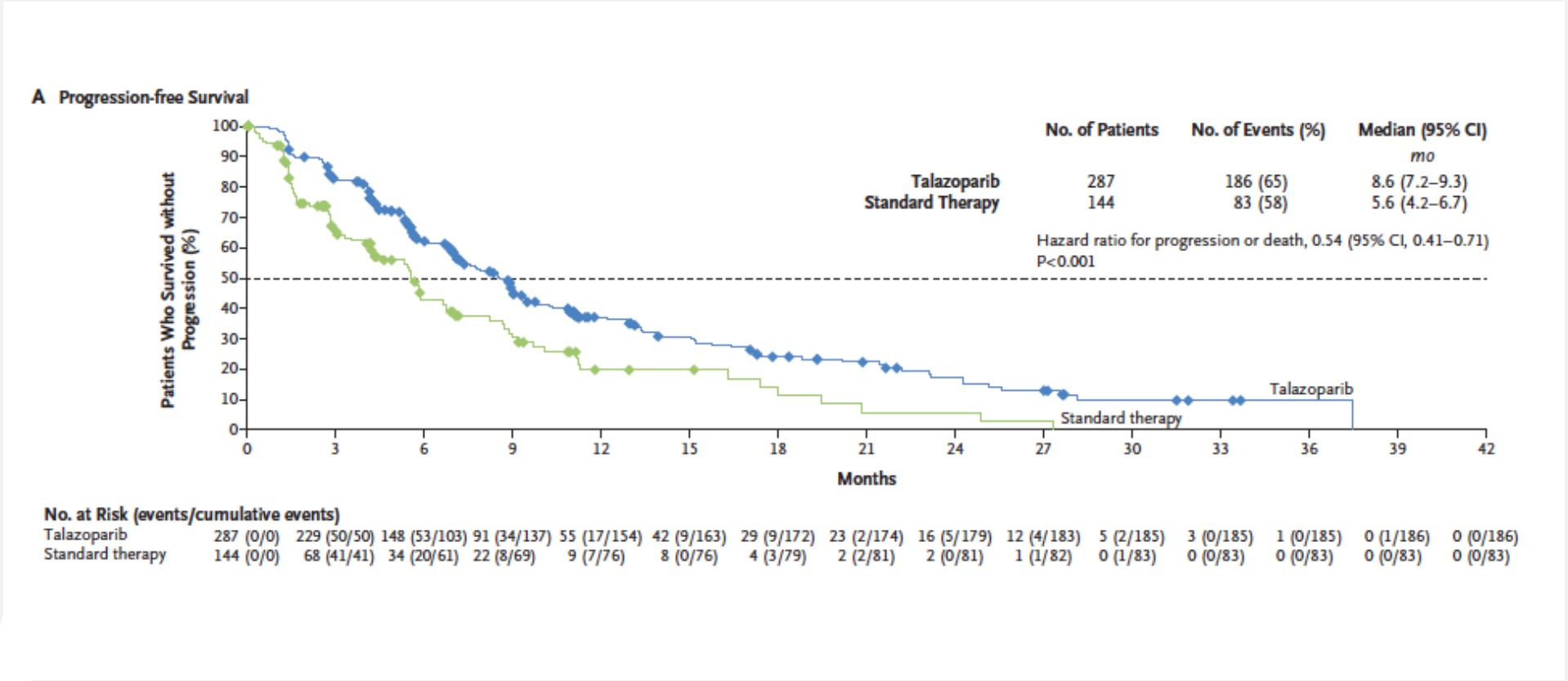
Olaparib in BRCA mBC – PFS





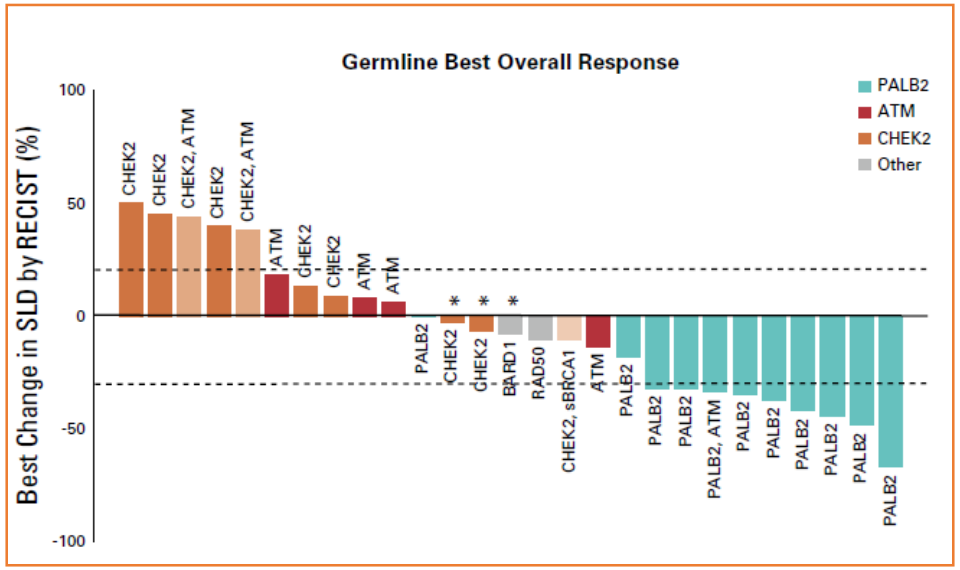
Robson ME, et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol. 2019 Apr 1;30(4):558-566.

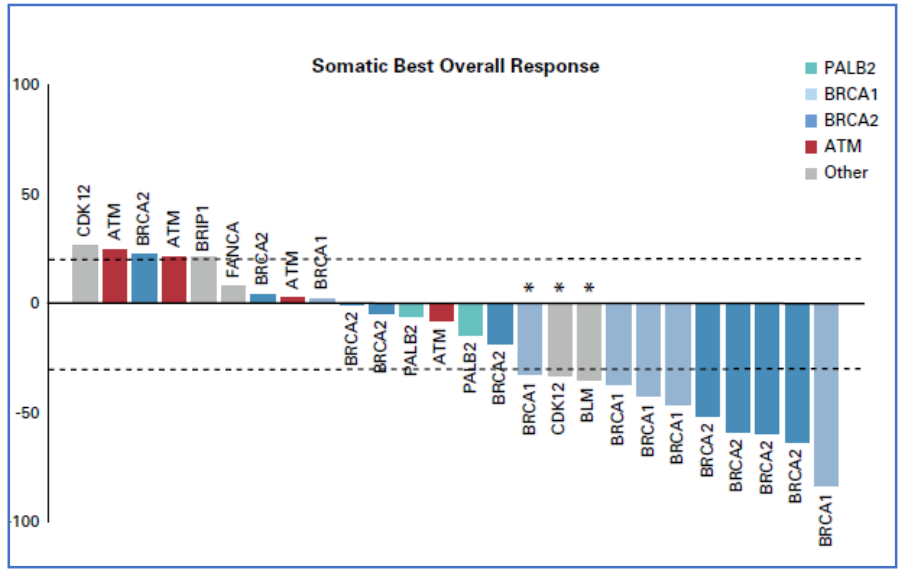
Talazoparib in BRCA mBC – PFS



Litton JK, et al. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. Ann Oncol. 2020 Nov;31(11):1526-1535.

TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes

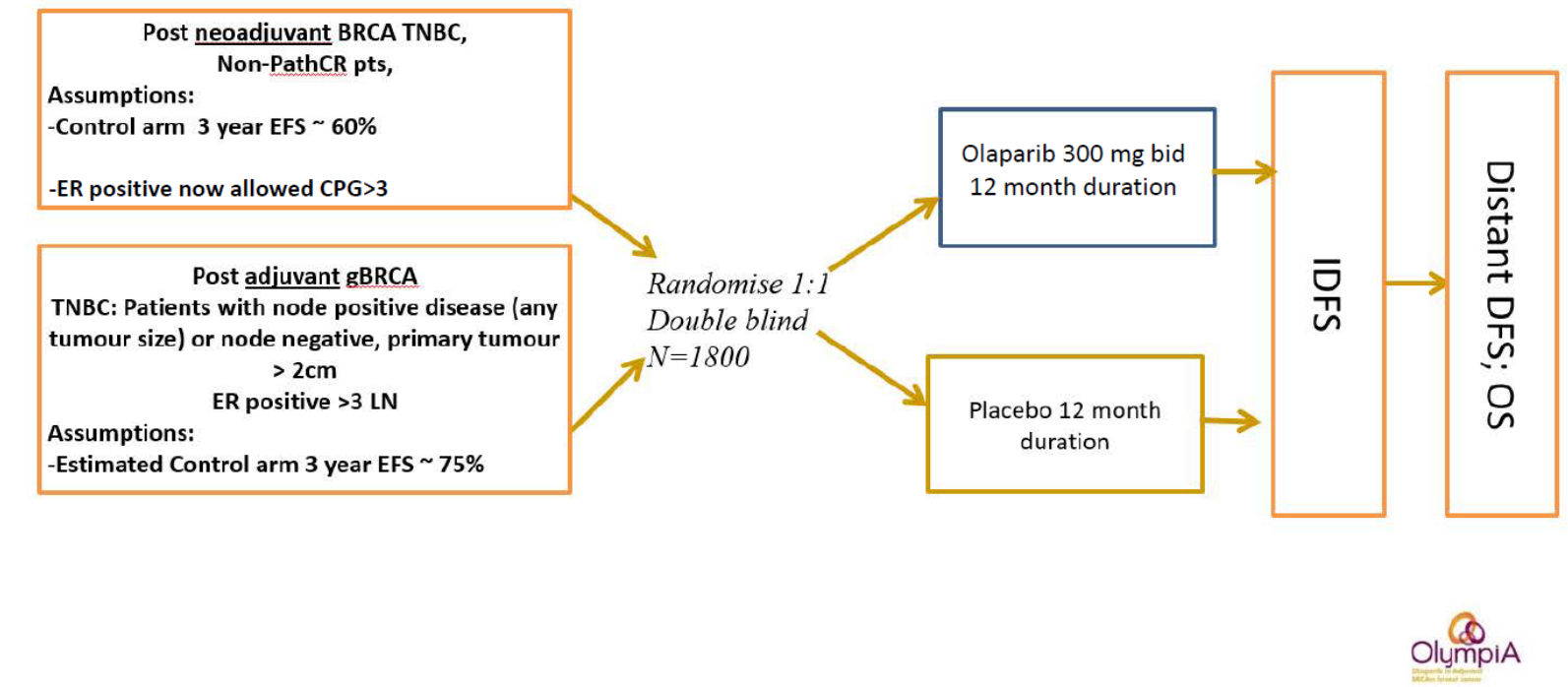




PALB2 N=13	sBRCA1/2 N=17^	ATM&CHEK2** N=17
Germline:)/11 PR (82%) 10/11 had tumor regression; 1 SD > 1 yr Somatic: 0/2 – both SD* (limited assessments)	8/16 PR (50%)	0/13 germline 0/4 somatic

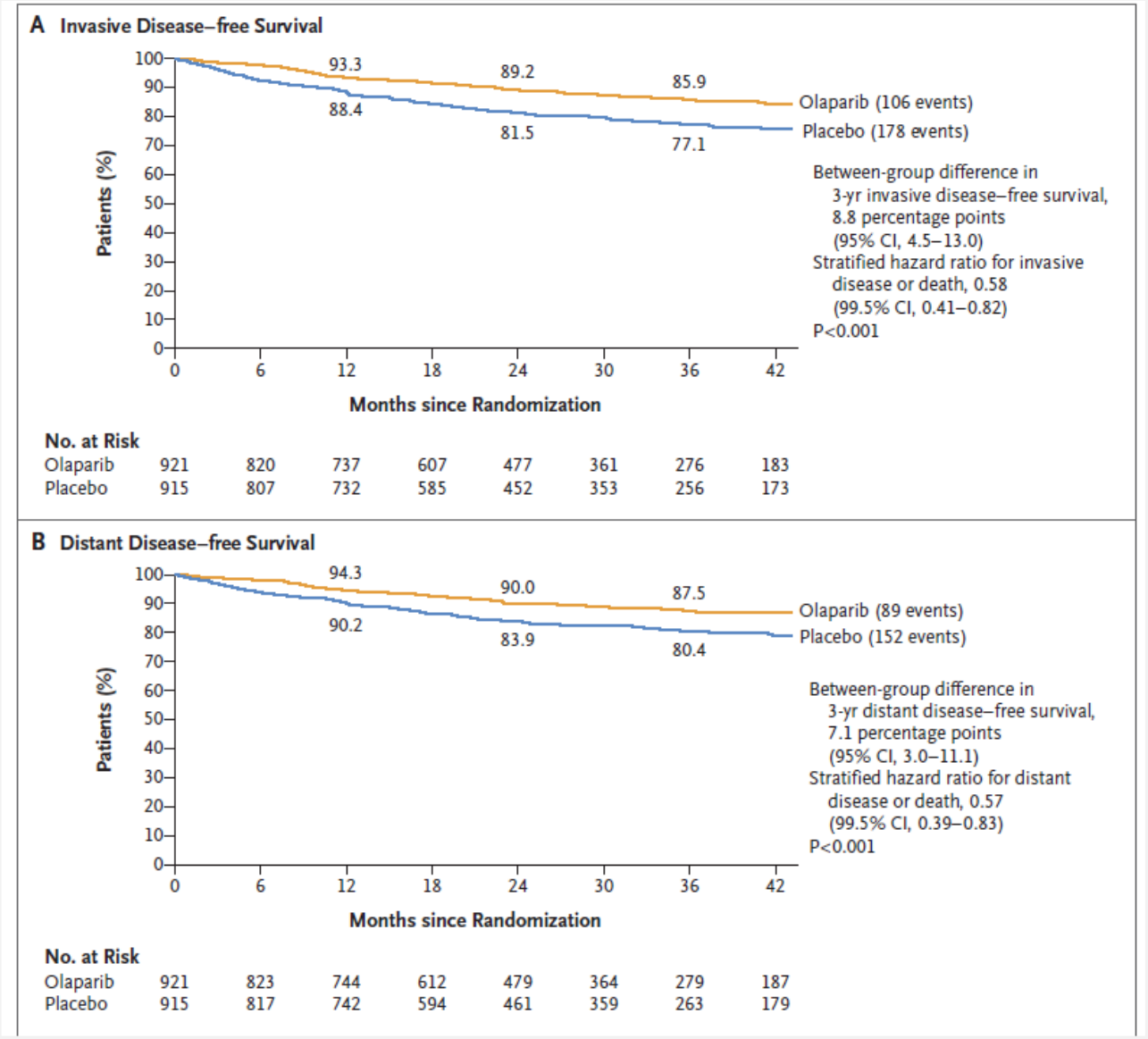
Tung NM, et al. Management of Hereditary Breast Cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Guideline. J Clin Oncol. 2020 Jun 20;38(18):2080-2106.

Adjuvant olaparib en gBRCA early BC patients at high risk of recurrence



Tutt ANJ, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021 Jun 24;384(25):2394-2405.

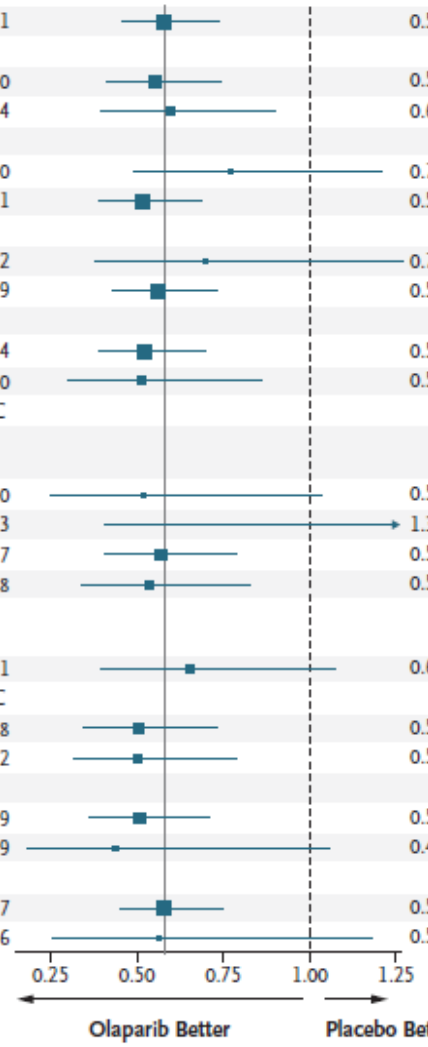
IDFS and DDFS



Tutt ANJ, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021 Jun 24;384(25):2394-2405.

Subgroup analysis

Subgroup	Olaparib	Placebo	3-Yr Invasive Disease–free Survival		Stratified Hazard Ratio for Invasive Disease or Death (95% CI)
			Olaparib	Placebo	
	no. of patients with an event/total no.		%		
All patients	106/921	178/915	85.9	77.1	0.58 (0.46–0.74)
Timing of previous chemotherapy					
Neoadjuvant	70/460	117/460	82.5	68.0	0.56 (0.41–0.75)
Adjuvant	36/461	61/455	89.3	85.4	0.60 (0.39–0.90)
Previous platinum-based chemotherapy					
Yes	34/247	43/239	82.0	77.0	0.77 (0.49–1.21)
No	72/674	135/676	87.3	77.1	0.52 (0.39–0.69)
Hormone-receptor status					
HR+ and HER2–	19/168	25/157	83.5	77.2	0.70 (0.38–1.27)
TNBC	87/751	153/758	86.1	76.9	0.56 (0.43–0.73)
Germline *BRCA* mutation					
BRCA1	70/558	126/558	85.0	73.4	0.52 (0.39–0.70)
BRCA2	22/230	38/209	88.6	78.0	0.52 (0.30–0.86)
BRCA1 and *BRCA2*	0/1	0/3	NC	NC	NC
Hormone-receptor status and timing of previous chemotherapy					
HR+ and HER2–, NACT	13/104	20/92	86.0	67.0	0.52 (0.25–1.04)
HR+ and HER2–, ACT	6/64	5/65	76.4	89.3	1.36 (0.41–4.71)
TNBC, NACT	57/354	97/368	81.4	67.7	0.57 (0.41–0.79)
TNBC, ACT	30/397	56/390	90.3	84.8	0.54 (0.34–0.83)
Previous platinum-based chemotherapy and timing of previous chemotherapy					
Yes, NACT	26/169	39/169	81.8	70.1	0.66 (0.40–1.07)
Yes, ACT	8/78	4/70	NC	NC	NC
No, NACT	44/291	78/291	83.1	66.8	0.51 (0.35–0.73)
No, ACT	28/383	57/385	90.4	84.2	0.51 (0.32–0.79)
CPS+EG score in patients with previous NACT					
Score of 2, 3, or 4	55/398	96/387	84.3	68.9	0.51 (0.37–0.71)
Score of 5 or 6	11/22	10/15	50.0	17.9	0.44 (0.19–1.06)
Primary database					
Breast International Group	95/810	160/806	86.0	76.7	0.58 (0.45–0.75)
NRG Oncology (United States)	11/111	18/109	85.0	80.6	0.57 (0.26–1.18)



Tutt ANJ, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021 Jun 24;384(25):2394-2405.

FDA/EMA approvals of PARPi

Tumor type	Treatment	Selection biomarker	Line	PARPi	PFS	HR	Reference
Ovarian Cancer	Monotherapy	gBRCA mut s/gBRCA mut	≥ 3-4L	olaparib rucaparib	9.4 (in pt-sensitive) 11.1 (in pt-sensitive)		Domcheck et al, Gynecol Oncol 2016 Oza et al, Gynecol Oncol 2017
	Maintenance	pt-sensitive pt-sensitive	Relapsed	olaparib niraparib rucaparib	8.4 vs. 4.8 months 21.0 vs 5.5 (gBRCA); 12.9 vs 3.8 (HRD+); 9.3 vs 3.9 (HRD-) 10.8 vs. 5.4 months	0.35 0.27; 0.38; 0.45 0.36	Lederman et al, Lancet Oncol 2014 & 2016 Mirza et al NEJM 2016 Coleman et al, Lancet 2017
	Maintenance	pt-response, s/gBRCA mut pt-response, s/gBRCA mut and/or HRD+ pt-response, all comers	1L	olaparib olaparib + beva niraparib	36 vs. 13.8 months 37.2 vs. 17.7 months 21.9 vs. 10.4 months	0.30 0.33 (0.43 in HRD+/BRCA-) 0.62 (0.43 in HRD+)	Moore et al, NEJM 2018 Ray-Coquard et al, NEJM 2019 González-Martín et al, NEJM 2019
Breast Cancer	Monotherapy	gBRCA mut gBRCA mut	≥ 3L	olaparib talazoparib	7.0 vs. 4.2 months 8.6 vs. 5.6 months	0.58 0.54	Robson et al, NEJM 2017 Litton et al, NEJM 2018
Pancreatic Cancer	Maintenance	gBRCA mut	1L	olaparib	7.4 vs. 3.8 months	0.53	Golan et al, NEJM 2019
Prostate Cancer	Monotherapy	tHRR gene mut/tBRCA mut s/gBRCA mut	Hormone-resistant	olaparib rucaparib	7.4 vs 3.6 months 8.1	0.34 (single arm)	de Bono et al, NEJM 2020 Abida et al, JCO 2020

For cancer risk assessment, genetic testing needs to be

Accompanied with counseling

Comprehensive

Low risk of uncertainty

For therapeutic decision-making, the genetic test needs to be

Fast

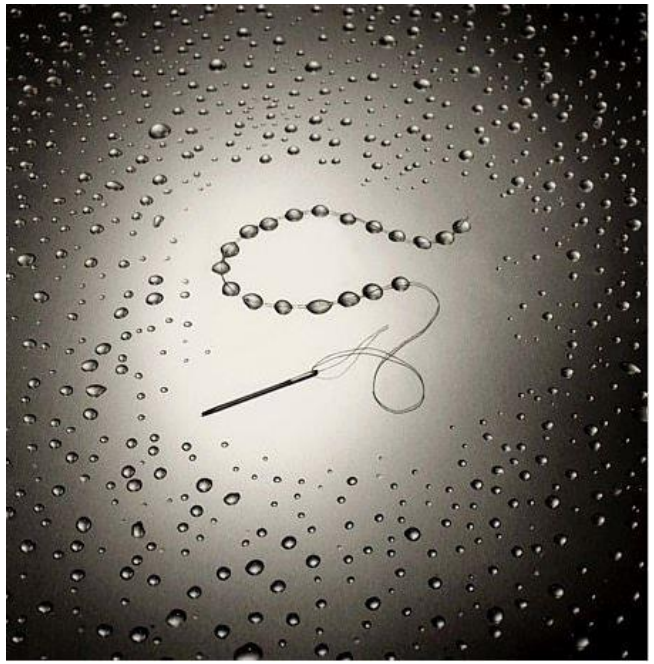
Accesible

Comprehensive

Take home messages

BRCA testing in breast cancer patients is NOT A CONVENTIONAL BIOMARKER:

- MRI-based protocols for BC screening
- Consider prophylatic mastectomy
- Recommend PBSO
- Impacts on reproductive decisions
- Predictive biomarker for targeted therapies



by Chema Madoz

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Thank you

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