Multigene assessment of genetic risk for multiple primary breast cancers

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JK, DT, KM, KS, KB, EH, SC and TS are employees of Myriad Genetics, Inc.; JS is currently an employee of Guardant Health and owns Myriad Genetics stocks. Other authors have no conflict of interests.

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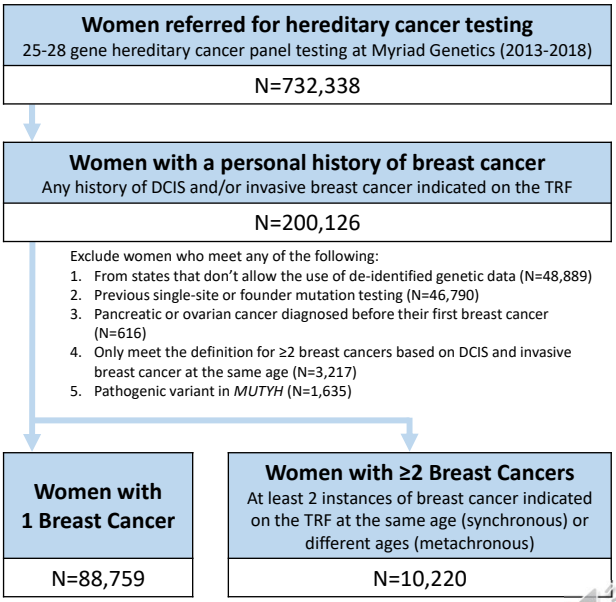
Background & Methods

- A better understanding of hereditary cancer risk for ≥2 breast cancers beyond the *BRCA1* and *BRCA2* genes is needed to improve personalized risk assessment and medical management.
- We assessed the risk of ≥2 breast cancers for all genes included in a multi-gene panel test.



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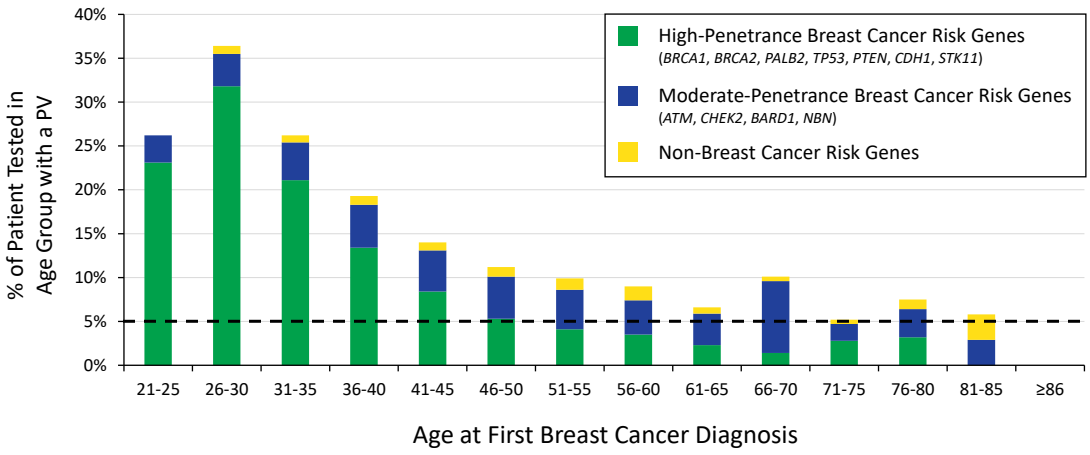
PV† prevalence remained ≥5% in all age groups



†Multiple PV carriers were omitted from analysis
Figure is based on a subset of women with 2+ breast cancers

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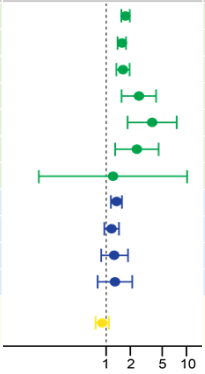
Among women with breast cancer, 7 genes were associated with a significantly increased risk for a 2nd breast cancer

Gene	≥ 2 Breast Cancers		1 Breast Cancer		Results from Multivariable Logistic Regression	
	N	% of Cohort	N	% of Cohort	Odds Ratio (95% CI)	p-value
Breast Cancer Risk Genes	1212	11.86	7165	8.07	**1.54 (1.44, 1.65)**	**<0.001**
BRCA1	359	3.51	1906	2.15	**1.74 (1.55, 1.97)**	**<0.001**
BRCA2	337	3.30	2007	2.26	**1.57 (1.39, 1.77)**	**<0.001**
PALB2	130	1.27	735	0.83	**1.62 (1.34, 1.96)**	**<0.001**
TP53	21	0.21	84	0.09	**2.56 (1.56, 4.20)**	**<0.001**
PTEN	13	0.13	26	0.03	**3.80 (1.88, 7.69)**	**<0.001**
CDH1	13	0.13	50	0.06	**2.42 (1.30, 4.52)**	**0.01**
STK11	1	0.01	8	0.01	1.22 (0.14, 10.35)	0.86
CHEK2	186	1.82	1236	1.39	**1.35 (1.15, 1.57)**	**<0.001**
ATM	102	1.00	772	0.87	1.17 (0.95, 1.45)	0.14
BARD1	30	0.29	212	0.24	1.27 (0.87, 1.87)	0.22
NBN	20	0.20	129	0.15	1.29 (0.78, 2.12)	0.32
Non-Breast Cancer Risk Genes	105	1.03	980	1.10	0.92 (0.75, 1.13)	0.45



Multivariable logistic regression models determined relative risk of multiple breast cancers conferred by pathogenic variants as odds ratios and 95% confidence intervals (CIs). All models accounted for age of diagnosis, personal and family cancer history, and ancestry. Multiple PV carriers were omitted from analysis.

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Conclusions

- Risk for two or more breast cancers was significantly elevated for several high- and moderate-penetrance breast cancer risk genes, affirming the association of two or more breast cancers with diverse genetic etiologies.
- Our findings suggest no clear decline in pathogenic variants in women with two or more breast cancers after age 50.
- **Multigene panel testing should be considered for all women with two or more breast cancers.**

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