Promoting Breast Cancer Screening after Multiplex Genetic Testing and Genetic Counseling

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BACKGROUND

- Cancer screening guidelines recommend that germline carriers with a pathogenic variant (PV) in a breast cancer susceptibility gene should undergo more intensive breast screening including breast magnetic resonance imaging (MRI).
- We assessed the impact of genetic counseling and multiplex genetic panel testing (MGPT) on adherence to recommended screening within 1 year after genetic testing.

METHODS

COHORT

- 2,000 patients were recruited between July 2014 and November 2016 at three medical centers: USC Norris, LAC, and Stanford.
- Patients were enrolled if they met standard clinical criteria for genetic testing or were predicted to have a ≥2.5% probability of inherited cancer susceptibility using validated prediction models.
- Patients completed self-administered questionnaires at 3, 6, and 12 months after genetic results disclosure.
- Patients underwent post-test genetic counseling during which personalized cancer screening recommendations were discussed, including breast cancer screening.

GENETIC TESTING

- All patients had testing with a multi-gene panel that included genes associated with breast cancer (*BRCA1, BRCA2, ATM, CHEK2, PALB2, NBN, BARD1, TP53, STK11,* and *CDH1*) as well as several genes associated with other cancer risks.
- Variants were classified using ACMG/AMP recommendations with supporting linkage, biochemical, clinical, functional, and statistical data used for specific missense and intronic alterations.

STATISTICAL ANALYSIS

- Multivariable logistic regression was used to analyze an association between MGPT result and breast MRI after adjusting for study center, personal history of breast cancer and personal history of breast surgery.

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NCCN GUIDELINES

- The NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian are listed in Table 1 (V1.2018).

Table 1. NCCN Breast MRI Screening Guidelines

Gene/Syndrome	Recommendation*
BRCA1* and *BRCA2	
BRCA1	MRI starting at age 25-29
BRCA2	MRI starting at age 25-29
Other High Risk Breast Cancer Genes	
CDH1	MRI starting at age 30
PALB2	MRI starting at age 30
TP53	MRI starting at age 20-29
Moderate Risk Breast Cancer Genes	
ATM	MRI starting at age 40
BRIP1	None
CHEK2	MRI starting at age 40
NBN	MRI starting at age 40
PTEN	MRI starting at age 30-35
RAD51C	None
RAD51D	None
STK11	MRI starting at age 25-29
Other Risk Breast Cancer Genes	
BARD1	None

*Or 5-10 years earlier than the youngest diagnosis in the family but not later than stated in the table or specific gene mutation

RESULTS

Table 2. Patient Characteristics*

Characteristic	USC Norris (N=797)	LAC (N=715)	Stanford (N=488)	Total (N=2,000)
Age, years				
Median (Range)	51 (16, 92)	49 (21, 92)	57 (17, 90)	51 (16, 92)
Gender, N (%)				
Female	591 (74.2%)	610 (85.3%)	413 (84.6%)	1,614 (80.7%)
Male	206 (25.8%)	105 (14.7%)	75 (15.4%)	386 (19.3%)
Ethnicity, N (%)				
Hispanic/Latino	166 (20.8 %)	554 (77.5%)	96 (19.7%)	816 (40.8%)
Non Hispanic/Latino	631 (79.2%)	157 (22.0%)	391 (80.1%)	1,179 (59.0%)
Unknown	0	4 (0.6%)	1 (0.2%)	5 (0.3%)
Personal Cancer History, N (%)				
Affected	549 (68.9%)	554 (77.5%)	348 (71.3%)	1,451 (72.6%)
Unaffected	248 (31.1%)	161 (22.5%)	140 (28.7%)	549 (27.4%)

*All characteristics were significantly different between sites (p<0.001)

Table 3. Summary of Patients with Pathogenic Variants in Breast Cancer-Risk Genes Undergoing Breast MRI within 1 Year of Multiplex Genetic Panel Testing

Gene	Patients with a PV	Carriers with Documented Breast MRI Results	Any Breast BIRADS >3	Underwent Diagnostic Biopsy	New Diagnosis of Cancer
BRCA1* and *BRCA2					
BRCA1	40	36 (88%)	5	2	2*
BRCA2	34	28 (78%)	5	1	0
Other High Risk Breast Cancer Genes					
CDH1	1	1 (100%)	0	0	0
PALB2	9	6 (67%)	1	1	1*
TP53	6	5 (83%)	1	0	0
Moderate Risk Breast Cancer Genes					
ATM	16	15 (94%)	2	1	0
CHEK2	17	11 (65%)	0	1	1**
NBN	2	2 (100%)	0	0	0
Other Risk Breast Cancer Genes					
BARD1	2	2 (100%)	0	0	0

*Invasive Ductal Adenocarcinoma; **Lobular Carcinoma In Situ

Table 4. Likelihood of Undergoing Breast MRI after Multiplex Genetic Panel Testing

	Multivariable		
Mutation	**Odds Ratio**	**95% CI**	**p-value**
Negative	1 (*ref*)	-	-
VUS	1.0	0.77, 1.35	0.906
PV in Any Gene	2.2	1.51, 3.27	<0.001
PV in Moderate Risk Breast Cancer Genes*	3.2	1.27, 7.98	0.013
PV in High Risk Breast Cancer Genes*	3.4	0.75, 15.60	0.112
PV in *BRCA1/2*	3.5	1.92, 6.20	<0.001
PV in Other Gene	1.2	0.64, 2.15	0.602

*See Table 1 for gene classification

Multivariable logistic regression analyses were adjusted for study center, personal history of breast cancer, and personal history of breast surgery; Patients with more than one pathogenic variant (PV) were excluded from analyses

Table 5. Summary of Patients with Pathogenic Variants in Other Genes

Gene	Patients with a PV	Breast MRI Recorded on Survey
APC	3	0/1
APC I1307K	15	3/10 (30%)
BRIP1	5	0/2
CDKN2A	1	0/1
EPCAM	1	1/1 (100%)
MLH1	8	0/3
MSH2	10	0/6
MSH6	8	1/4 (25%)
MUTYH (biallelic)	2	0/1
MUTYH (monoallelic)	40	8/23 (35%)
PMS2	10	2/7 (29%)
RAD51C	4	1/4 (25%)
RAD51D	4	1/2 (50%)

3 patients with PVs in multiple genes are missing breast MRI information: *MLH1* and *APC* I1307K, *MLH1* and *PMS2*, *BRCA2* and monoallelic *MUTYH*

- 2,000 patients completed MGPT and 1,532 (77%) completed at least one follow-up survey.
- 242 (12%) tested positive for at least 1 PV in any gene.
  - 127 (6%) patients tested positive for at least 1 PV in a breast cancer risk gene (Table 3).
- Within 1 year, patients with a PV were more likely to undergo MRI versus those testing negative (p<0.001; Table 4).
- Patients with a PV in *BRCA1/2* (p<0.001) or a moderate risk breast cancer gene (*CHEK2, ATM, NBN*) (p=0.013) were three times more likely to have MRI versus those testing negative (Table 4).
- Patients with a PV in other high risk breast cancer genes (*PALB2, TP53,* or *CDH1*) were three times more likely to undergo MRI (p=0.112) versus those testing negative, but the results did not reach statistical significance (Table 4).
- There was no difference in Breast MRI (p=0.906) use among those with a variant of uncertain significance (VUS) versus those with negative results (Table 4).

CONCLUSIONS

- MGPT and genetic counseling prompted appropriate adoption and adherence to breast cancer screening among patients with a PV in *BRCA1/2*.
- There was no difference in screening between those with VUS or negative results.