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Unaffected Women and Genetic Testing for Hereditary Breast Cancer: To Test or not to Test?

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BACKGROUND

- National Comprehensive Cancer Network (NCCN) guidelines recommend genetic testing for family members affected with cancer be prioritized over testing for unaffected family members.[1]
- Testing affected family members first followed by unaffected close family members is not always possible.
- Less is known about the results of genetic testing for hereditary cancer in healthy women.
- This study aims to describe the results of two different breast cancer focused multi-gene panels (MGP) in women without cancer and assess for meeting NCCN *BRCA1/2* testing criteria.

METHODS

- Eligible cases included all females with breast cancer or with no personal history of cancer, tested with either a 6 gene or a 17 gene breast cancer-focused MGP between June 2013 and June 2016.
- Personal and family history information was extracted from test request forms for analysis.
- Cases with positive results were assessed to determine whether they met NCCN *BRCA1/2* testing criteria.

RESULTS

- 21,057 women tested with the 6-gene MGP, BRCAplus (Figure 1)
  - 5471 unaffected, 2.9% (n=156) tested positive for a gene mutation
  - Mutations in *BRCA1/2* were the most common in both affected and unaffected women (Table 1)
- 31,525 women tested with the 17-gene MGP, BreastNext (Figure 2)
  - 6714 unaffected, 5.9% (n=399) tested positive for a gene mutation
  - Mutations in *CHEK2* were the most common in both affected and unaffected women (Table 2)
- 507 unaffected women had positive results from either BRCAplus or BreastNext (Figure 3)
  - 91.5% (n=464) of positive, unaffected women met NCCN *BRCA1/2* testing criteria
    - N=460 met criteria based on family history
    - N=4 had a known familial mutation but insufficient family history per our database
  - 8.5% (N=43) of positive, unaffected women did not meet NCCN *BRCA1/2* testing criteria
    - One of these individuals did meet NCCN criteria for Lynch syndrome genetic testing

TAKE-HOME POINTS

- In our cohort, the vast majority of unaffected women undergoing MGP testing met NCCN guidelines for *BRCA1/2* genetic testing.
- If providers are not utilizing the NCCN criteria to screen patients, high risk unaffected women may not be identified and, therefore, not receive recommendations for increased screening and/or risk reducing measures.
- Our cohort is biased toward including patients who meet NCCN guidelines for genetic testing as a prerequisite for insurance coverage. Additional studies are needed to confirm these results in broader, clinic-based cohort.

REFERENCES

1. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian (Version 2.2016). https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Accessed December 1, 2016.

Figure 1 Percentages and Types of BRCAplus Results in Patients With and Without Cancer

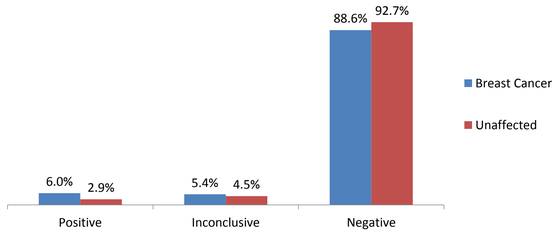

Figure 2 Percentages and Types of BreastNext Results in Patients With and Without Cancer

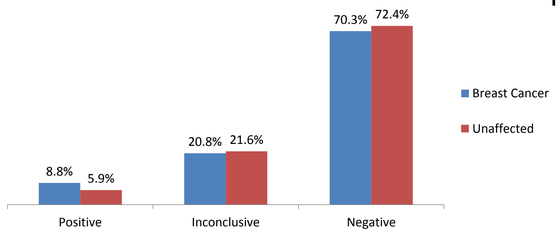

Figure 3 NCCN Criteria for *BRCA1/2* Testing in Unaffected Women (N=507)

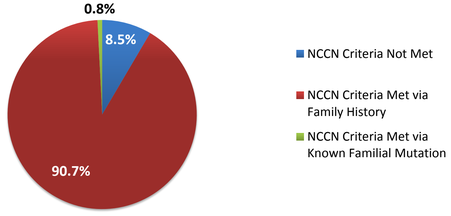

Table 1: BRCAplus Positive Patients Mutation Spectrum

	Affected w/ Breast Cancer		Unaffected	
Gene	N	%	N	%
BRCA1	426	45.6%	72	46.1%
BRCA2	379	40.6%	67	42.9%
TP53	68	7.3%	6	3.9%
CDH1	12	1.3%	5	3.2%
*PALB2**	25	2.7%	4	2.6%
PTEN	23	2.5%	2	1.3%
Total Positive	933		156	

**PALB2* added to BRCAplus 10/1/15 – only 208 cases tested

Table 2: BreastNext Positive Patients Mutation Spectrum

	Affected w/ Breast Cancer		Unaffected	
Gene	N	%	N	%
CHEK2	694	24.8%	121	21.8%
MUTYH carrier	379	13.6%	112	20.2%
BRCA2	363	12.9%	79	14.2%
BRCA1	313	11.2%	60	10.8%
ATM	304	10.9%	49	8.8%
PALB2	243	8.7%	26	4.7%
RAD50	66	2.4%	21	3.8%
BRIP1	69	2.5%	15	2.7%
BARD1	60	2.2%	15	2.7%
NBN	53	1.9%	13	2.3%
RAD51D	24	0.9%	12	2.1%
NF1	51	1.8%	10	1.8%
RAD51C	40	1.4%	7	1.3%
MRE11A	34	1.2%	7	1.3%
TP53	67	2.4%	5	0.9%
CDH1	16	0.6%	2	0.4%
PTEN	18	0.6%	1	0.2%
Biallelic *MUTYH*	1	0.0%	0	0.00%
Total Positive	2795		555	

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Category II, D: Breast Cancer Genetics/Screening
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Background:
The National Comprehensive Cancer Network (NCCN) guidelines recommend that genetic testing start with a family member affected with cancer, if available. While this process is the most informative, it can be complicated by family dynamics, poor communication, non-testing of affected family members, and other factors. As a result, a growing number of women unaffected with cancer are receiving genetic testing, but little is known about the results of genetic testing in this group. This study aims to describe unaffected women tested with a breast-focused multi-gene panel (MGP) and assessed for meeting NCCN *BRCA1/2* testing criteria.

Methods:
Personal and family history information from females who had either a 6 gene or 17 gene breast-focused MGP between June 2013 and June 2016 were extracted from test request forms and clinic notes and evaluated. Cases with positive results were assessed for meeting NCCN *BRCA1/2* testing criteria.

Results:
Of 21,057 women tested with a 6 gene MGP, 26.0% were unaffected, and 2.9% (n=156) of those unaffected women tested positive for a gene mutation. Of 31,525 women tested with a 17 gene MGP, 21.3% were unaffected, and 5.9% (n=399) of those unaffected women tested positive. Combining positive results for unaffected women from both tests, 507 individuals were assessed using NCCN *BRCA1/2* testing criteria. The majority (91.5%, n=464) of positive, unaffected women met criteria. The vast majority (n=460) met criteria based on family history, while the remaining 4 individuals had a known familial mutation but insufficient family history per our database. Criteria were not met by 8.5% (n=43) of unaffected women with positive results; however, one of these individuals did meet NCCN criteria for Lynch syndrome genetic testing.

Conclusions:
NCCN guidelines recommend increased screening and/or risk reducing measures for women at high risk of developing breast and ovarian cancer due to a germline mutation. However, high risk unaffected women may not be appropriately identified if providers are not utilizing the NCCN criteria to screen their patients. Our data demonstrate that these criteria are able to identify the vast majority of mutation carriers in an unaffected laboratory patient population, and providers should consider utilizing these guidelines to screen their unaffected patients. Additional studies are needed to confirm these results in a broader, clinic-based cohort.