Prevalence of *BRCA1/2*-Negative Women Who Qualify for Adjunctive Breast MRI Screening

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BACKGROUND

- The National Comprehensive Cancer Network (NCCN) and the American Cancer Society (ACS) recommend breast MRI in addition to mammography for women with an estimated lifetime risk of breast cancer >20%.[1,2]
- Originally, this recommendation applied to women identified using breast cancer risk models "largely dependent on family history", and women identified with pathogenic variants (PVs) in the high-penetrance breast cancer risk genes: *BRCA1*, *BRCA2*, *PTEN*, *TP53*, *CDH1* and *STK11*.
- Recently, NCCN expanded the breast MRI recommendation to women identified as carrying PVs in the genes *ATM*, *CHEK2* and *PALB2*,[1] based on the estimated >20% lifetime breast cancer risk associated with these genes.

OBJECTIVE

- This analysis compares the proportion of women identified as having a >20% lifetime risk for breast cancer as an outcome of genetic testing for *BRCA1* and *BRCA2* versus expanded testing utilizing a panel that includes the genes *ATM*, *CHEK2* and *PALB2*.
- We also determined the percentage of women identified with PVs in *ATM*, *CHEK2* and *PALB2* who would have been identified as having a >20% risk based on family history assessement alone.

METHODS

Genetic Testing

- All data were derived from clinical testing ordered for 45,661 female patients over a 1 year period from September 2013 to November 2014.
- Women were tested using a 25-gene hereditary cancer panel that includes *BRCA1*, *BRCA2*, *ATM*, *CHEK2*, and *PALB2* (Table 1).
- Testing included full sequencing and comprehensive large rearrangement analysis, except for *EPCAM* (large rearrangement only).
- PVs are those that received a laboratory classification of Deleterious or Likely Deleterious.

Table 1. 25-Gene Hereditary Cancer Panel

Genes	Associated Cancers
BRCA1, BRCA2	Breast, Ovarian, Pancreatic, Prostate
ATM	Breast, Pancreatic
CHEK2	Breast
PALB2	Breast, Pancreatic
Other Panel Genes	
APC, BARD1, BMPR1A, BRIP1, CDH1, CDK4, CDKN2A, EPCAM, MLH1, MSH2, MSH6, MUTYH (biallelic), *NBN, PMS2, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53*	

Family History Assessment

- All clinical information was obtained from the test request form.
- The Claus model was applied to women carrying PVs in *ATM*, *CHEK2*, and *PALB2* to determine which patients would have been identified as having a >20% risk of breast cancer based on family history alone.
- The Claus tables provide a lifetime risk, defined as to age 80, based on the breast cancer history in a woman's first and second-degree relatives.[3]
- Affected individuals were assigned a risk estimate without consideration of existing diagnoses in order to determine if they would have been identified for more aggressive screening prior to their breast cancer.
- For the purposes of this analysis, the Claus tables were used to estimate a lifetime risk for a woman at age 29, without adjusting for her current age. This is analogous to how risk estimates are applied for patients with risk due to PVs in inherited breast cancer genes, which are not typically adjusted for age.
- This results in an over-estimate of women identified as having a >20% risk based on family history, as risk estimates based on the tables decline as women age.

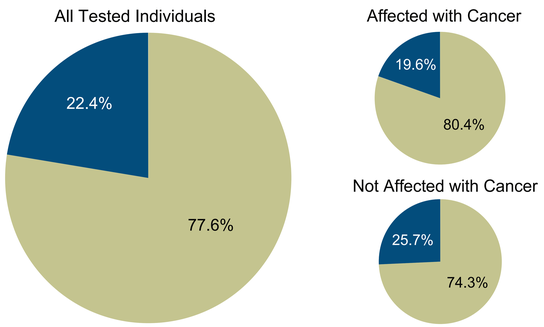
RESULTS

Table 2. Breakdown of *ATM, CHEK2* and *PALB2* Pathogenic Variants and Claus Assessment for Female Carriers

Gene	Observations	Patients with Breast Cancer	Patients with estimated risk >20% based on family history*
ATM	315	167 (53.0%)	63 (20.0%)
CHEK2	379	185 (48.8%)	80 (21.1%)
PALB2	229	147 (64.2%)	63 (27.5%)
ATM* & *CHEK2	2	0	2
ATM* & *PALB2	2	0	1
CHEK2* & *PALB2	5	5	0
Total	932	504 (54.1%)	209 (22.4%)

Note: Percentages were calculated according to gene. Percentages were not calculated for rows with fewer than 10 patients.
* Based on Claus model, without including personal diagnosis of tested patient

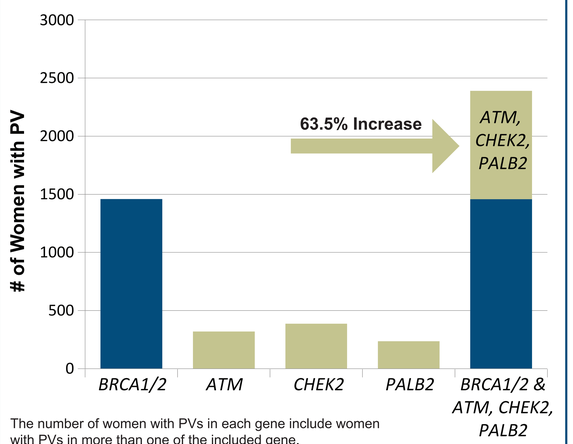
Figure 1. Proportion of Women with a PV in *ATM*, *CHEK2*, or *PALB2* Who Would Have Been Candidates for Breast MRI Based on Family History Assessment



Excludes women who also carried a PV in *BRCA1/2;* Based on Claus model, does not include personal diagnosis of patient

- 932 women were identified as carrying PVs in only *ATM*, *CHEK2*, or *PALB2* (Table 2).
  - 9 women carried PVs in 2 of these genes.
  - 16 patients with a second PV in *BRCA1* or *BRCA2* were excluded from analysis.
- Only 209 (22.4%) of these women reached the >20% lifetime breast cancer risk threshold using the Claus tables (Figure 1).
  - This demonstrates that family history alone will not identify the majority of women with PVs in *ATM*, *CHEK2*, and *PALB2*.
- The percentage of unaffected female PV carriers meeting the >20% risk threshold (25.7%) was higher than that for affected patients (19.6%) (Figure 1).
  - This is consistent with the presumption that unaffected patients would require a stronger family history to be considered appropriate candidates for testing.
- 1,467 women were identified as carrying a PV in *BRCA1* or *BRCA2*.
  - The use of panel testing to detect PVs in *ATM*, *CHEK2*, and *PALB2* resulted in a 63.5% increase over the total found in *BRCA1* and *BRCA2* (Figure 2).

Figure 2. Distribution of Pathogenic Variants and the Increase in Testing Sensitivity from Including *ATM*, *CHEK2*, and *PALB2*



The number of women with PVs in each gene include women with PVs in more than one of the included gene.

CONCLUSIONS

- Relative to *BRCA1* and *BRCA2* testing alone, we found that clinical testing with a hereditary cancer risk panel that includes *ATM, CHEK2*, and *PALB2* in this cohort resulted in a 63.5% increase in the identification of women who are eligible for MRI screening.
- Close to 80% of the women with mutations in *ATM*, *CHEK2* and *PALB2* would not have been identified as having a >20% lifetime breast cancer risk based on family history assessment alone.

REFERENCES

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3. Claus E. B., Risch N., Thompson W. D. *Cancer*, 1994; 73: 643-651.

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