Genetic Testing Contributes Significantly to Improved Identification of Women Eligible for Increased Breast Cancer Screening Compared to Remaining Lifetime Risk Models Alone

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BACKGROUND

- Increased screening, including breast MRI, is recommended for women carrying pathogenic variants (PVs) in certain breast cancer risk genes, as well as women with an estimated remaining lifetime risk of breast cancer >20% using validated models based on clinical risk factors.
- We determined the extent to which genetic testing identifies women as appropriate candidates for increased screening who would not have been identified through evaluation of clinical factors, i.e., as represented by the well-validated and widely used Tyrer-Cuzick (TC) model.

METHODS

- We evaluated 100,318 women who had clinical genetic testing for suspicion of hereditary breast cancer risk between June 2017 and June 2018.
- Testing was performed with a 28-gene pan-cancer panel including 5 established breast cancer risk genes for which there are National Comprehensive Cancer Network (NCCN) guidelines for increased screening (e.g., breast MRI) -- *BRCA1, BRCA2, ATM, CHEK2,* and *PALB2* (see Table 1 for details).[1]
- A remaining lifetime breast cancer risk estimate was calculated using TC V 7.02 for all eligible women.[2]
- Eligibility for TC score calculation:
  - *Female*
  - *Unaffected with breast cancer*
  - *<85 years of age*
  - *Test Request Form with relevant TC data submitted*
  - *No indication of PV in a breast cancer gene in a relative*
- Risk estimates were calculated entering the *BRCA1/2* status as unknown.
- PVs are those variants with a laboratory classification of Deleterious or Suspected Deleterious.
- Women were not included in the analysis if they were found to have a PV in more than one gene, including any of the other 23 genes included in the panel testing.

Table 1. Characteristics of the 5 breast cancer risk genes included in this study

Gene	Estimated Lifetime Breast Cancer Risk	Other Cancer Risks	NCCN Breast MRI Recommendation
BRCA1	46%-87%	Ovarian, Prostate, Pancreatic	YES
BRCA2	43%-84%	Ovarian, Prostate, Pancreatic, Melanoma	YES
ATM	17%-52%	Pancreatic	YES
CHEK2	23%-48%	Colorectal	YES
PALB2	17%-58%	Pancreatic	YES

RESULTS

- 4,640 (4.6%) women carried a PV in one of the five genes, with 57% in *BRCA1* or *BRCA2*, and 43% in *ATM*, *CHEK2* or *PALB2* (Figure 1A).
- Among women with a PV, 1,479 (31.9%) had a diagnosis of breast cancer, and 407 (8.8%) were ineligible for TC for another reason.
- The distribution of PVs among the 2,754 women eligible for TC was similar to that in the entire cohort (Figure 1B).
- A TC risk estimate was calculated for the 2,754 women, 41.5% of whom did not meet the 20% threshold (Figure 2).
- Women with PVs in *BRCA1* were the least likely to have a TC score <20% and those with PVs in *BRCA2* and *ATM* were the most likely to fall below the 20% threshold (Figure 2).
- The % of women not meeting the TC 20% remaining lifetime risk threshold increases with age for carriers of PVs in the study genes (Figure 3).
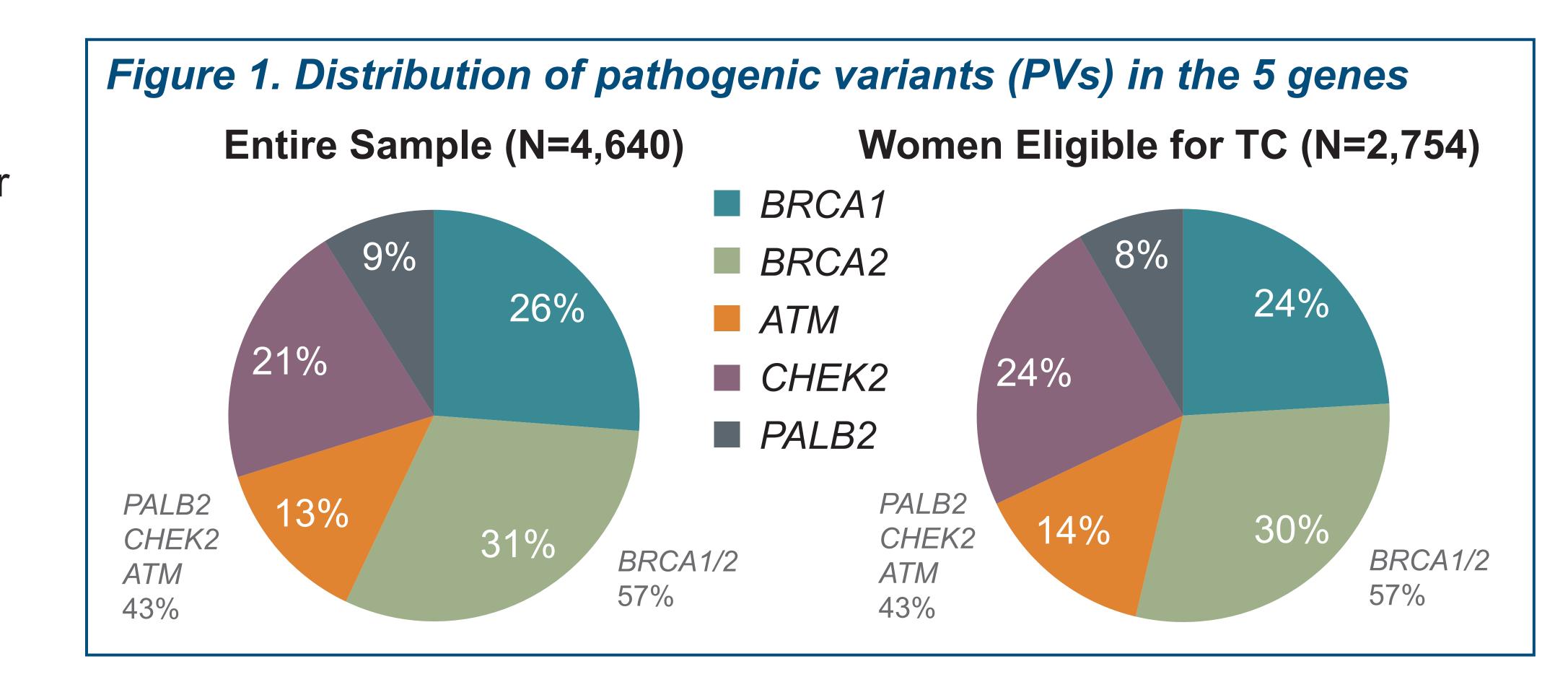
Figure 1. Distribution of pathogenic variants (PVs) in the 5 genes

Entire Sample (N=4,640)
BRCA1 26%, BRCA2 31%, ATM 13%, CHEK2 21%, PALB2 9%; BRCA1/2 57%, PALB2 CHEK2 ATM 43%

Women Eligible for TC (N=2,754)
BRCA1 24%, BRCA2 30%, ATM 14%, CHEK2 24%, PALB2 8%; BRCA1/2 57%, PALB2 CHEK2 ATM 43%

Figure 2. A remaining lifetime threshold of 20% fails to identify 40% of women eligible for increased screening due to PVs in BC risk genes.
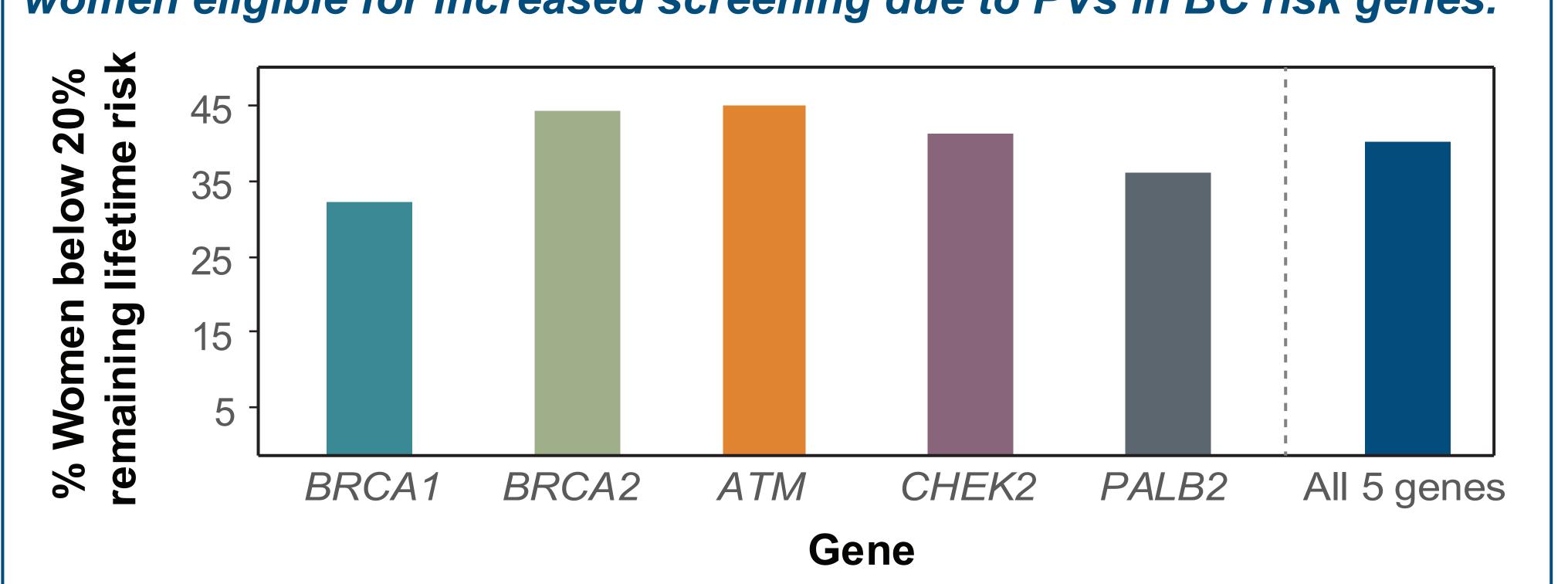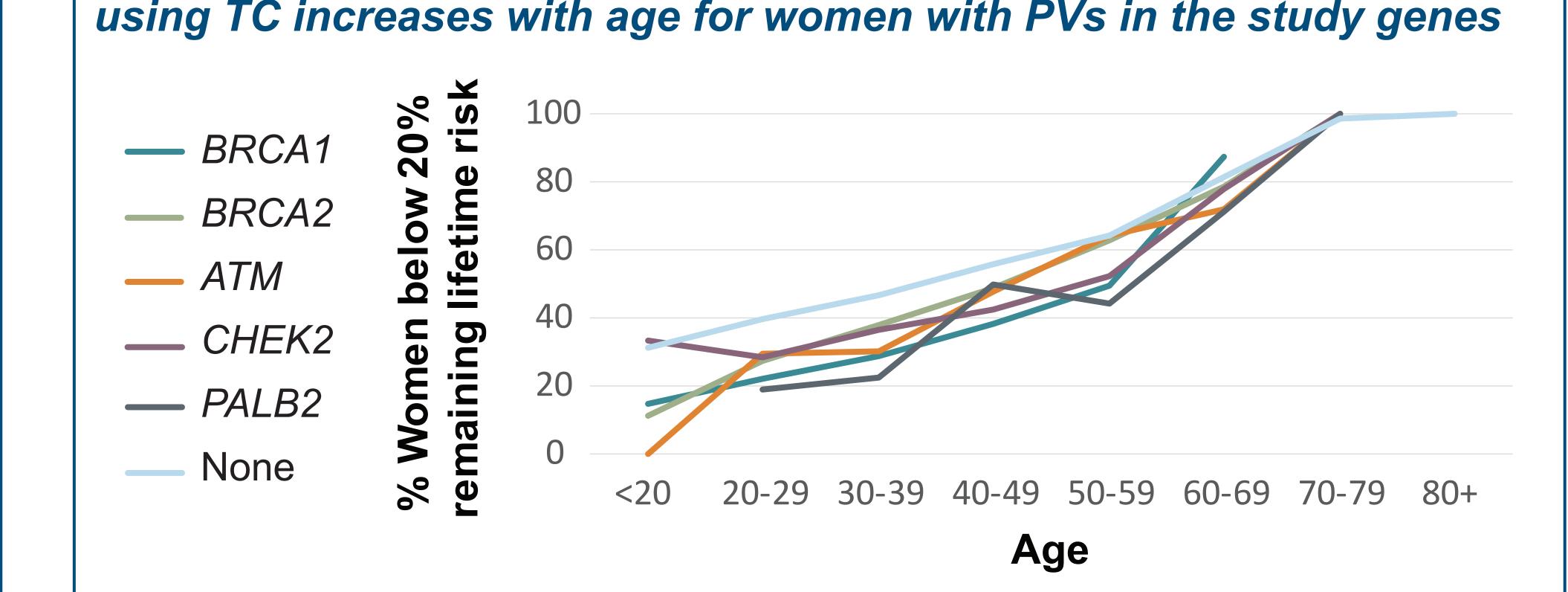

Table 2. Women carrying PVs in breast cancer risk genes with remaining lifetime risk of breast cancer estimated at <20% by Tyrer-Cuzick (TC)

Age at time of testing	*BRCA1* (N=663)	*BRCA2* (N=816)	*ATM* (N=393)	*CHEK2* (N=652)	*PALB2* (N=230)	Total (N=2,754)
<20	4 / 27 (14.8%)	1 / 9 (11.1%)	0 / 5 (0%)	1 / 3 (33.3%)	0 / 0 (0%)	6 / 44 (13.6%)
20-29	42 / 191 (22.0%)	42 / 154 (27.3%)	13 / 44 (29.5%)	31 / 109 (28.4%)	9 / 47 (19.1%)	137 / 545 (25.1%)
30-39	56 / 195 (28.7%)	96 / 252 (38.1%)	30 / 99 (30.3%)	67 / 184 (36.4%)	14 / 62 (22.6%)	263 / 792 (33.2%)
40-49	53 / 138 (38.4%)	98 / 201 (48.8%)	61 / 128 (47.7%)	79 / 186 (42.5%)	27 / 54 (50.0%)	318 / 707 (45.0%)
50-59	39 / 79 (49.4%)	89 / 142 (62.7%)	54 / 84 (64.3%)	68 / 130 (52.3%)	20 / 45 (44.4%)	270 / 480 (56.2%)
60-69	28 / 32 (87.5%)	41 / 52 (78.8%)	23 / 32 (71.9%)	28 / 36 (77.8%)	15 / 21 (71.4%)	135 / 173 (78.0%)
70-79	0 / 14 (0%)	6 / 6 (100.0%)	1 / 1 (100.0%)	4 / 4 (100.0%)	1 / 1 (100.0%)	12 / 26 (46.2%)
80+	1 / 1 (100.0%)	0 / 0 (0%)	0 / 0 (0%)	0 / 0 (0%)	0 / 0 (0%)	1 / 1 (100.0%)
All ages	223 / 663 (33.6%)	373 / 816 (45.7%)	182 / 393 (46.3%)	278 / 652 (42.6%)	86 / 230 (37.4%)	1,142 / 2,754 (41.5%)

N=Total number of PV carriers in cohort who were eligible for TC.
Each gene column shows the percentage of women with a PV in the gene who were eligible for TC, but who did not meet the 20% remaining lifetime risk threshold.

Figure 3. Likelihood a woman will have a remaining lifetime risk <20% using TC increases with age for women with PVs in the study genes

CONCLUSIONS

- Genetic testing for *ATM, CHEK2,* and *PALB2* significantly increases the number of women identified at increased risk compared to testing for *BRCA1* and *BRCA2* alone.
- In this analysis, clinical history-based factors failed to identify approximately 40% of the women eligible for high-risk breast cancer screening due to PVs in breast cancer risk genes. This demonstrates that risk models based on clinical factors alone will fail to identify a significant fraction of women who are candidates for modified medical management.
- There are only slight differences in the performance of the TC model in assessing risk for women with PVs in each of the 5 different genes analyzed in this study, even though these genes are associated with a wide range of breast cancer risks.
- Women are much less likely to meet a threshold of 20% remaining lifetime risk for breast cancer as they grow older. It may be desirable to re-evaluate using a threshold based on remaining lifetime risk, since this dramatically reduces the likelihood that high-risk women will be flagged for increased screening at older ages, when their immediate risk of a breast cancer diagnosis is likely to be highest. Thresholds based on shorter term risk estimates (i.e., ≥2-fold increased risk over the general population at any age) may be more clinically appropriate.

REFERENCES

1. Daly M et al. NCCN Clinical Practice Guidelines in Oncology®: Genetic/Familial High-Risk Assessment: Breast and Ovarian. V 2.2019. July 30. Available at http://www.nccn.org
2. Tyrer-Cuzick model Version 7.02 is available for download at the EMS-Trials website: http://www.ems-trials.org/riskevaluator/