

Detection of Pathogenic Mutations in Moderate Penetrance Breast Cancer Genes Significantly Increases the Number of Patients Identified as Candidates for Increased Screening

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BACKGROUND

Pathogenic mutations in the genes *ATM*, *CHEK2* and *PALB2* are considered to be of moderate/intermediate penetrance for inherited breast cancer risk, and are also known to increase risks for additional cancers (i.e., pancreatic, colorectal). However, clinical testing for these genes has not been widely incorporated into assessment of inherited breast cancer risk. Resistance to the adoption of clinical testing for these genes is largely based on the absence of professional society guidelines for medical management of mutation carriers. There is also a perception that female carriers of mutations in these genes can readily be identified as being at an increased risk for breast cancer based on family history alone, and therefore the identification of mutation carriers provides little clinical benefit.

Although there are currently no professional society guidelines that explicitly provide medical management recommendations for women carrying pathogenic mutations in *ATM*, *CHEK2* and *PALB2*, there are existing guidelines for women with an estimated lifetime breast cancer risk greater than 20%. These include initiation of screening at younger ages, at more frequent intervals, and with breast MRI in addition to mammography.² While these recommendations were originally based on risk estimates obtained from family history-based models, it seems reasonable to infer that they should also apply to risks arising from genetic factors.

We sought to demonstrate the potential value of clinical testing for mutations in these genes by analyzing outcomes from clinical testing with a 25-gene hereditary cancer panel including these 3 genes, as well as *BRCA1*, *BRCA2*, and 4 other genes associated with breast cancer risk and for which management guidelines exist (*CDHI*, *PTEN*, *STK11*, *TP53*). We also determined what proportion of *ATM*, *CHEK2* and *PALB2* mutation carriers would have been flagged for appropriate breast cancer risk reduction interventions based on family history alone. The findings demonstrate that the testing for these 3 genes increases the number of women identified as candidates for more aggressive medical management compared with either testing for only those genes traditionally thought of as high penetrance, or by ascertaining patients solely on the basis of family history.

METHODS

GENETIC TESTING

- All data was derived from clinical testing ordered using a 25-gene hereditary cancer panel between 09/04/2013 and 06/12/2014. The panel included *ATM*, *CHEK2*, *PALB2*, *BRCA1*, *BRCA2*, *CDHI*, *PTEN*, *STK11*, and *TP53*.
- Variants were considered to be pathogenic if they were classified as Deleterious or Suspected Deleterious using our laboratory's classification system, which is based on guidelines from the American College of Medical Genetics and Genomics (ACMG).^{3,4}

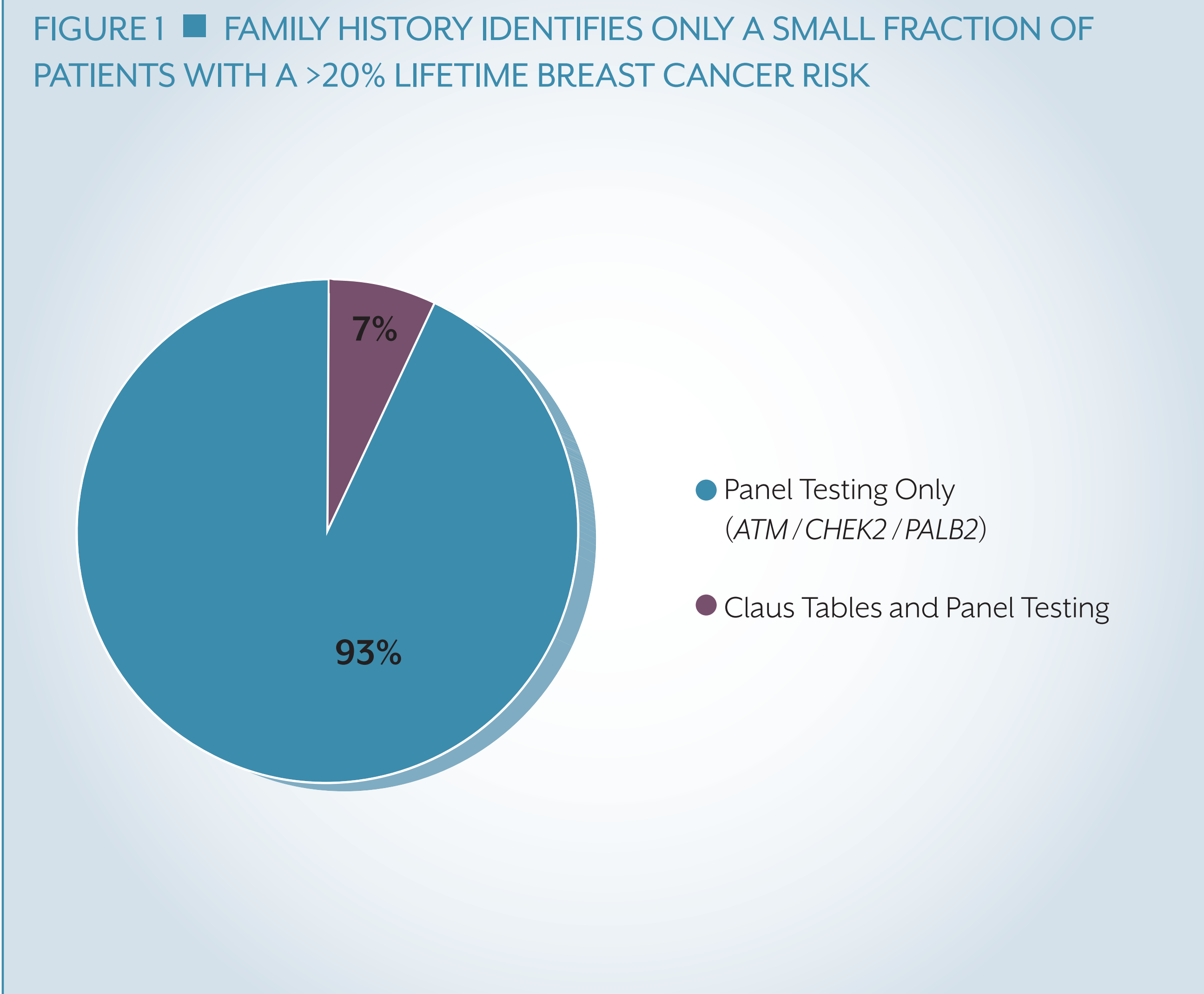
FAMILY HISTORY ASSESSMENT

- The Claus model was used to determine which tested patients would have been identified as having a >20% lifetime (to age 80) breast cancer risk based on the reported family history.³
- Affected individuals were assigned a risk estimate without consideration of existing diagnoses, as the goal was to determine if they would have been identified for more aggressive screening prior to their breast cancer diagnosis.
- All patient personal and family history information was obtained from test requisition forms completed by providers.

RESULTS AND CONCLUSIONS

- Pathogenic mutations in the intermediate penetrance genes *ATM*, *CHEK2* and *PALB2* increase the lifetime risk of female breast cancer above the 20% threshold at which guidelines for modified medical management apply (Table 1).

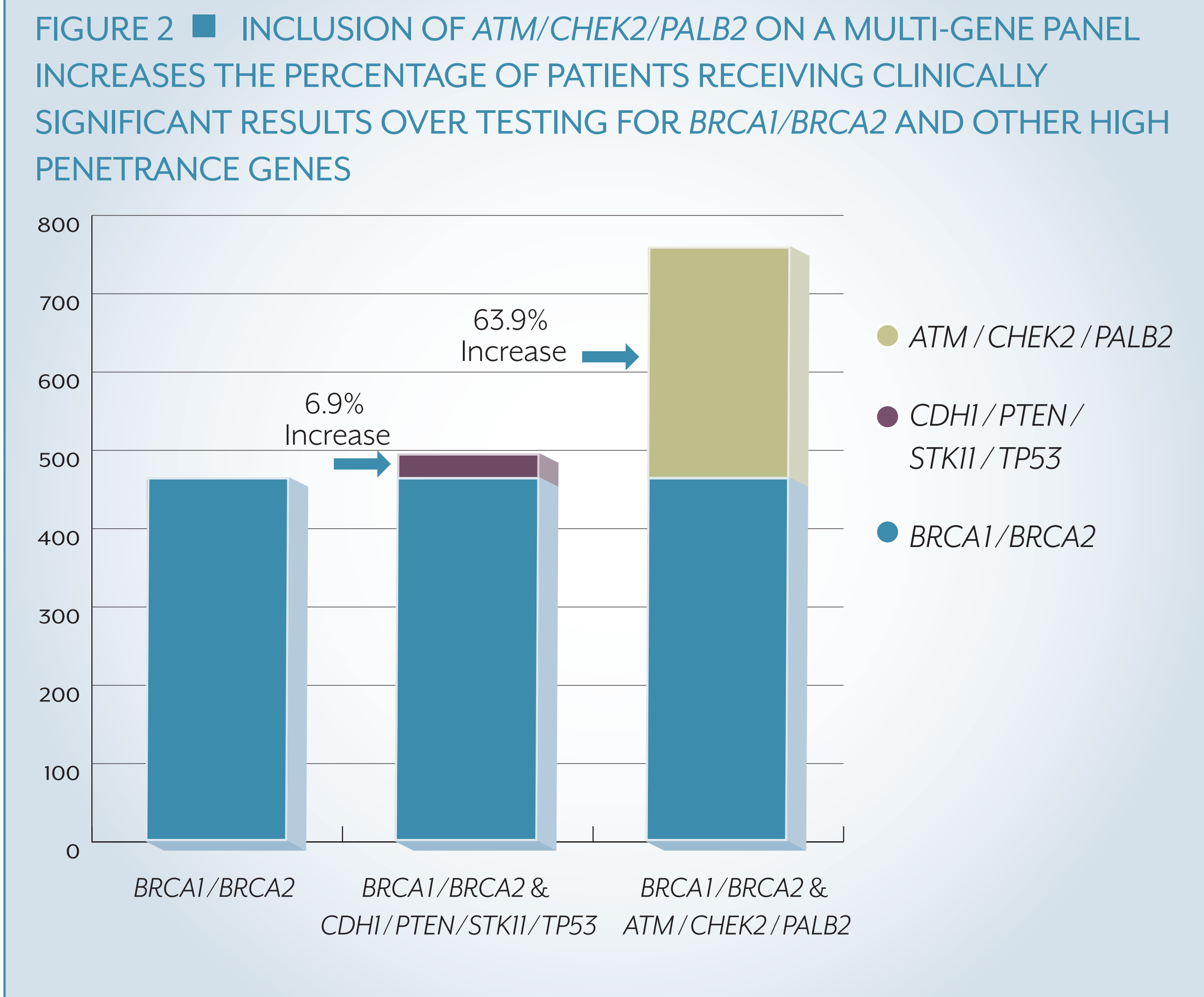
TABLE 1 ■ SUMMARY OF GENES AND CANCER RISKS*			
Gene	Female Breast Cancer Risk (to age 80)	Other Cancer Risks	Associated Recessive Condition
<i>ATM</i>	17% - 52%	Pancreatic	Ataxia Telangiectasia (AT)
<i>CHEK2</i>	23% - 48%	Colorectal Male Breast Prostate	N/A
<i>PALB2</i>	20% - 40%	Male Breast Pancreatic	Fanconi Anemia (FANCN)
* Citations supporting the cancer risks provided in this table are available at www.myriadpro.com/myrisk/why-myriad-myrisk/gene-selection/ or by contacting Myriad Genetic Laboratories at helpmed@myriad.com			



- Inclusion of these 3 genes in a hereditary cancer gene panel increases the sensitivity of the testing (i.e., identification of women who are candidates for modified medical management) by 63.9% over testing only for *BRCA1* and *BRCA2*, and by 59.8% over testing only for *BRCA1* / *BRCA2* plus *TP53*, *PTEN*, *CDHI*, and *STK11* (Figure 2).

- The majority of women in whom mutations in these genes are identified would not have been identified based on family history alone (Table 2 and Figure 1).

TABLE 2 ■ BREAKDOWN OF <i>ATM</i> , <i>CHEK2</i> AND <i>PALB2</i> MUTATIONS AND CLAUSS ASSESSMENT FOR MUTATION CARRIERS		
Gene	Observations*	Patients with estimated risk >20% based on family history**
<i>ATM</i>	108	8 (7.4%)
<i>CHEK2</i>	114	7 (6.1%)
<i>PALB2</i>	70	6 (8.6%)
<i>ATM</i> & <i>CHEK2</i>	0	N/A
<i>ATM</i> & <i>PALB2</i>	1	1 (100%)
<i>CHEK2</i> & <i>PALB2</i>	3	0
Total	296	22 (7.4%)
*Excludes seven patients who also had a mutation in <i>BRCA1</i> or <i>BRCA2</i> (three <i>ATM</i> / <i>BRCA1</i> , three <i>ATM</i> / <i>BRCA2</i> , one <i>BRCA1</i> / <i>PALB2</i>)		
**Based on Claus model		



- Identification of mutations in these genes has the potential to provide information to guide management for risks of cancers other than breast. For example, 6 of the 70 (8.6%) women identified with mutations in *PALB2* met CAPS (Cancer of the Pancreas Screening Consortium) guidelines for consideration of pancreatic cancer screening, as they had a 1st-degree relative with this malignancy.

REFERENCES

- Beyers TB et al. NCCN Clinical Practice Guidelines in Oncology®: Breast Cancer Screening and Diagnosis. V 2.2013. July 3. Available at <http://www.nccn.org>.
- Saslow D, et al. CA Cancer J Clin. 2007 Mar-Apr;57(2):75-89. Erratum in: CA Cancer J Clin. 2007 May-Jun;57(3):185. PubMed PMID: 17392385.
- Richards CS, et al. Genet Med. 2008 Apr;10(4):294-300. doi: 10.1097/GIM.0b013e31816b5cae. PubMed PMID: 18414213.
- Egginton JM, et al. Clin Genet. 2014 Sept;86(3):229-37. PubMed PMID: 24304220.
- Claus EB, et al. Cancer. 1994 Feb 1;73(3):643-51. PubMed PMID: 8299086.

