SPECTRUM OF MUTATIONS IDENTIFIED IN A 25-GENE HEREDITARY CANCER PANEL FOR PATIENTS WITH BREAST CANCER

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BACKGROUND

- Breast cancer is recognized as a component tumor in several well-described hereditary cancer syndromes, including Hereditary Breast and Ovarian Cancer (HBOC). Current National Comprehensive Cancer Network (NCCN) guidelines help identify patients with personal and/or family histories that should be tested for individual hereditary cancer syndromes; however, complex and limited patient histories can make it difficult to identify appropriate genetic testing.
- Advancements in next-generation sequencing allow health care providers to test for mutations in multiple cancer-predisposing genes simultaneously. This approach is especially useful in breast cancer patients, as there are many genes associated with increased breast cancer risk.
- The focus of this analysis was to determine the spectrum of gene mutations observed in patients with a personal history of breast cancer.

METHODS

- A commercial laboratory database was analyzed for patients with a personal diagnosis of breast cancer who underwent a 25-gene hereditary cancer panel between September 2013 and November 2014.
- The panel included BRCA1, BRCA2, TP53, PTEN, MLH1, MSH2, MSH6, PMS2, EPCAM, APC, BMPR1A, CDH1, CDKN2A, MUTYH, SMAD4, STK11, CHEK2, PALB2, ATM, NBN, BARD1, BRIP1, CDK4, RAD51C and RAD51D.
- Sequencing and large rearrangement were performed for all genes in the panel except *EPCAM*, for which only large rearrangement analysis was performed. All patient data regarding clinical history was obtained by health care provider report on the test requisition forms.

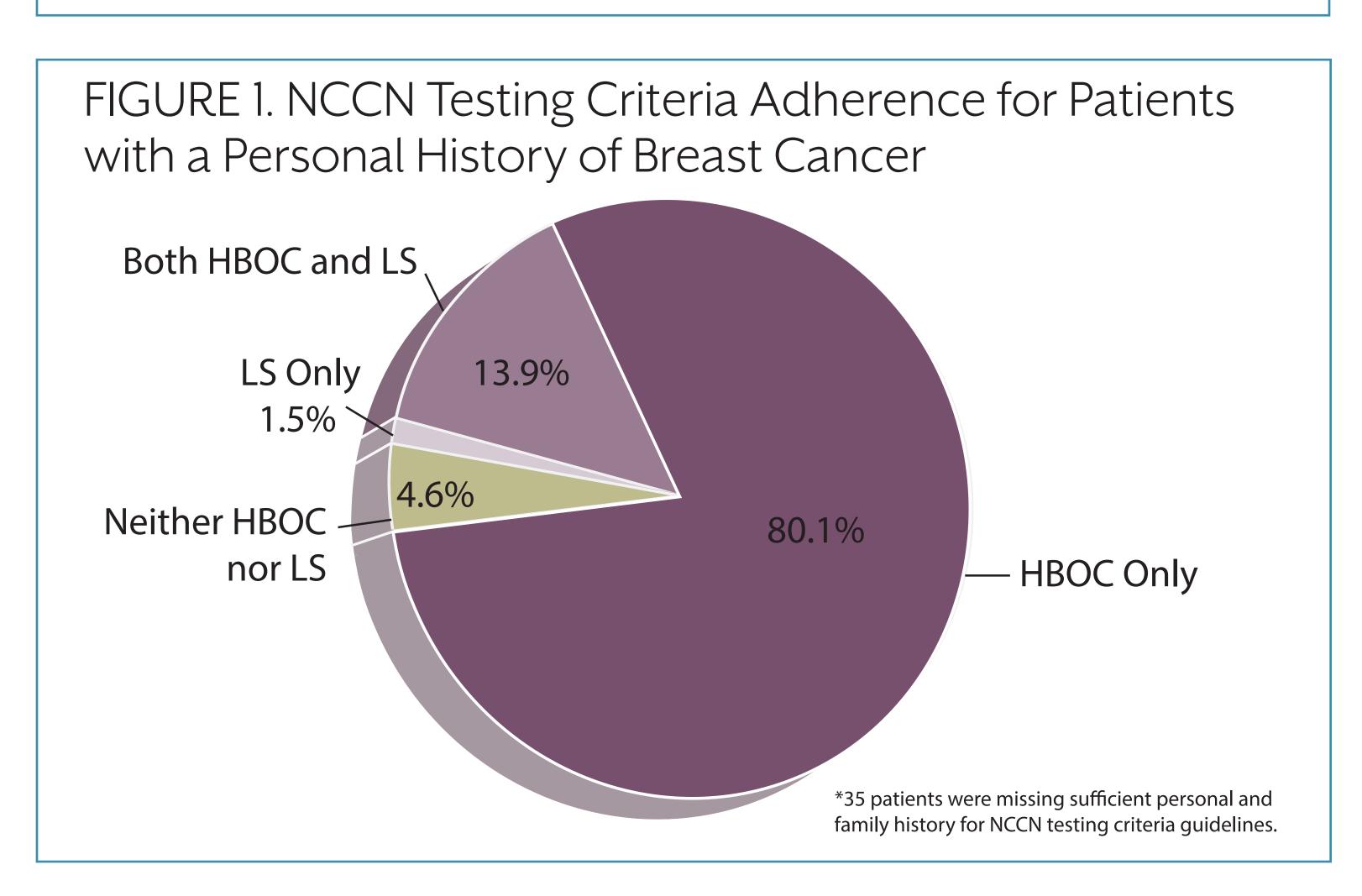
TABLE 1. Mutation Distribution in Patients With a Personal History of Breast Cancer*

Mutations in

Mutations in Males

	Females (N=1,652)		(N=33)	
	n	%	n	%
Genes Associated with Breast Cancer				
BRCA1	408	24.7%	2	6.1%
BRCA2	388	23.5%	26	78.8%
CHEK2	191	11.6%	1	3%
ATM	174	10.5%	1	3%
PALB2	153	9.3%	0	0%
BRIP1	46	2.8%	1	3%
BARD1	39	2.4%	1	3%
RAD51C	34	2.1%	0	0%
TP53	26	1.6%	0	0%
NBN	25	1.5%	1	3%
PTEN	9	0.5%	0	0%
CDH1	8	0.5%	0	0%
Genes Not Associated with Breast Cancer				
PMS2	44	2.7%	0	0%
MSH6	40	2.4%	0	0%
MSH2	16	1.0%	0	0%
CDKN2A	15	0.9%	0	0%
RAD51D	11	0.7%	0	0%
MLH1	10	0.6%	0	0%
APC	9	0.5%	0	0%
Biallelic MUTYH	3	0.2%	0	0%
EPCAM	2	0.1%	0	0%
SMAD4	1	0.1%	0	0
ncludes mutations from 45 patients who have 2 mutations.				

*Includes mutations from 45 patients who have 2 mutations. Does not include 73 *APC/1307K* mutations.



RESULTS

- A total of 17,142 patients with a personal history of breast cancer were identified with 9.5% of females (n=1,608) and 16.2% of males (n=32) being positive for at least one deleterious or suspected deleterious mutation (Table 1, Figure 2).
- 48.9% of mutations were detected in HBOC genes (BRCA1 and BRCA2).
- 42.1% of mutations were detected in other genes associated with breast cancer (Table 1).
- o 6.6% of mutations were detected in Lynch syndrome (LS) genes (MLH1, MSH2, MSH6, PMS2, EPCAM).
- 2.3% of mutations were detected in other genes not associated with breast cancer (APC, MUTYH, RAD51D, CDKN2A, SMAD4).
- 45 patients were identified with two mutations. *BRCA1* or *BRCA2* accounted for at least one of the mutations in 31 patients.



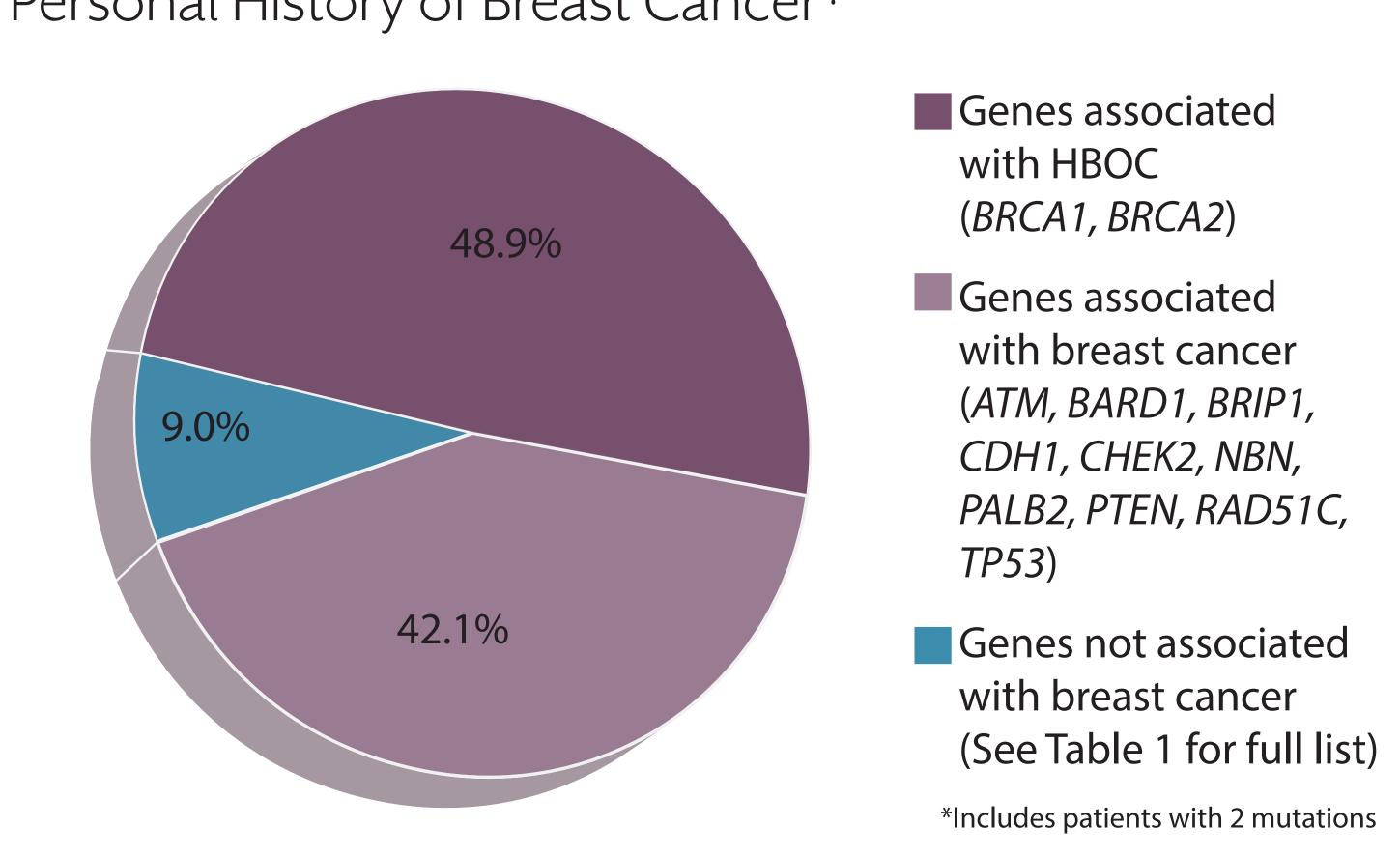
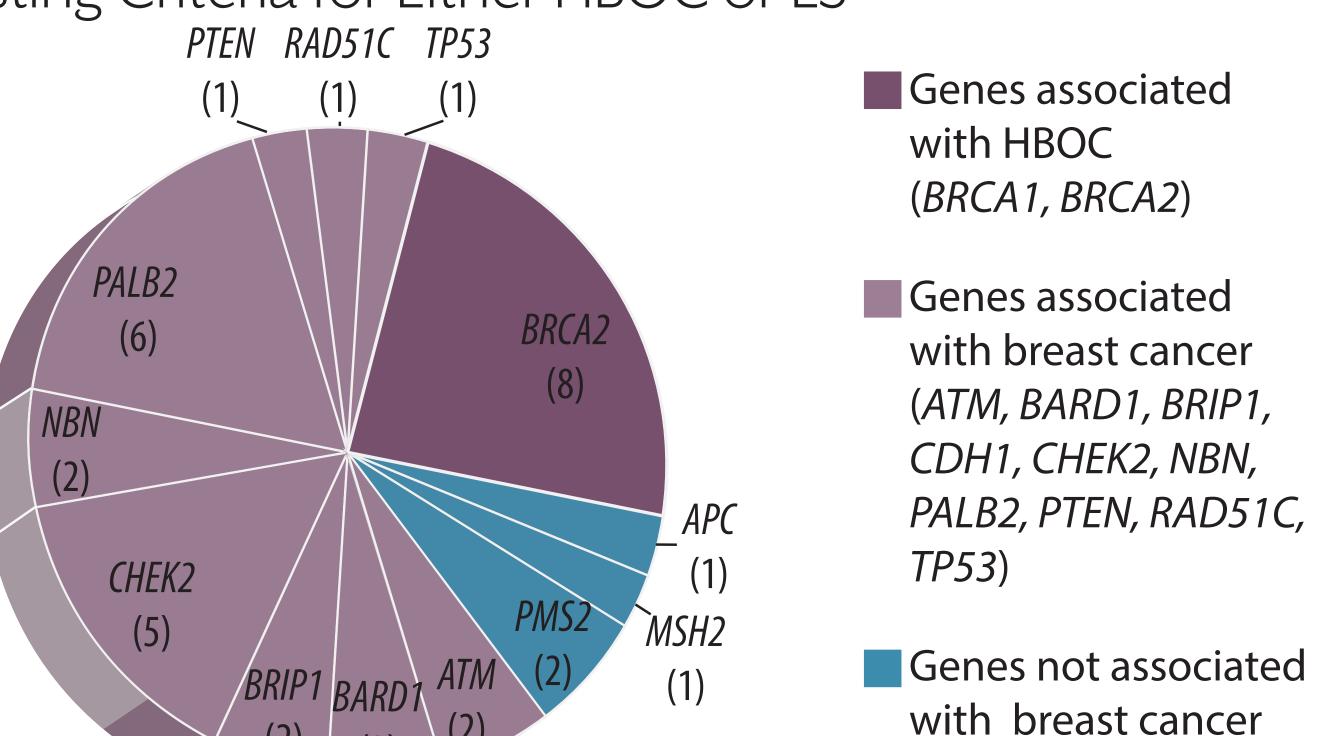
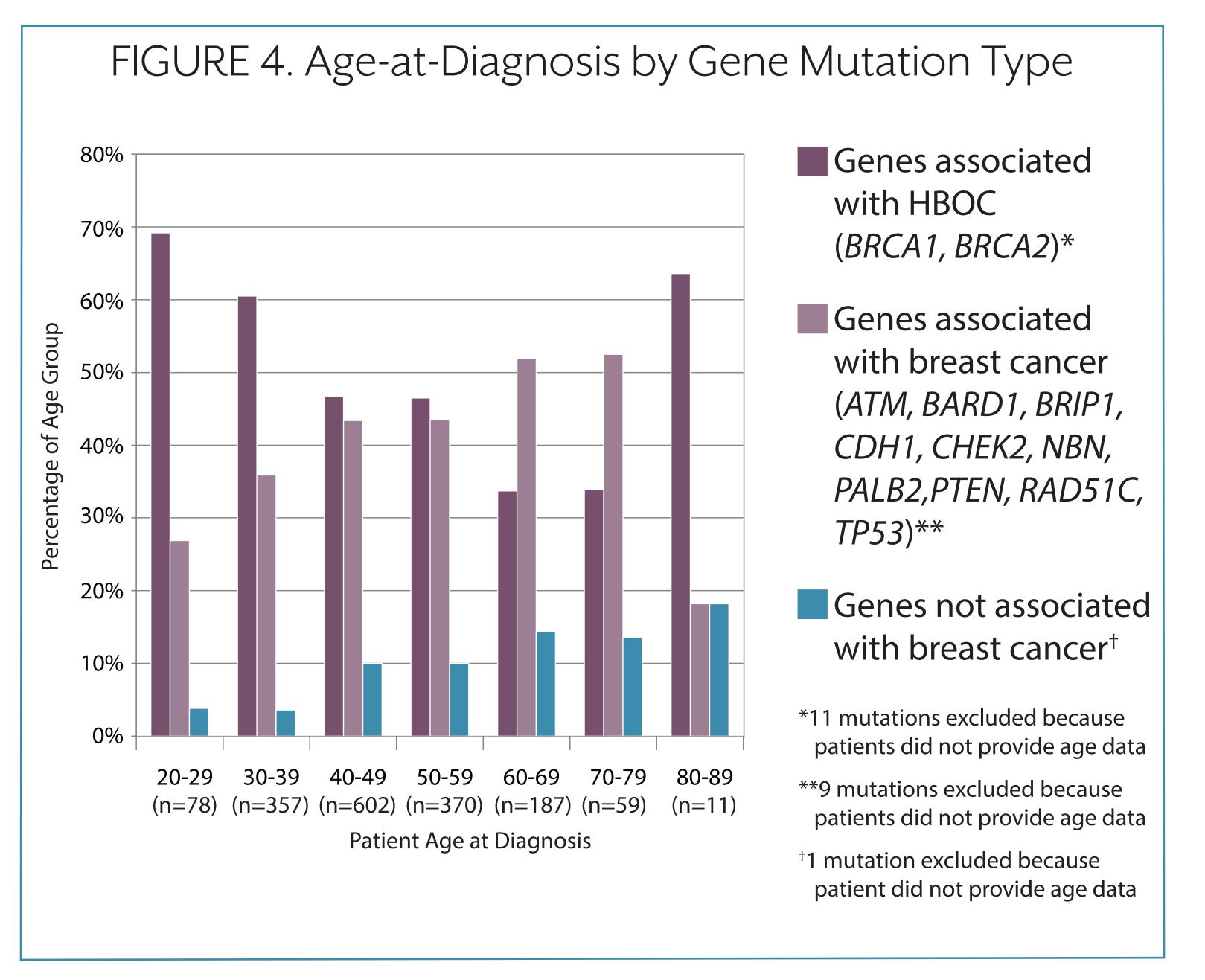


FIGURE 3. Mutations in Patients Who Did Not Meet NCCN Testing Criteria for Either HBOC or LS



- The majority of patients were diagnosed between the ages of 40 and 59.
- Figure 4 shows the distribution of mutations corresponding to patient age at diagnosis in 10-year intervals.
- The majority of mutation positive patients diagnosed with breast cancer before age 40 were identified as having a mutation in *BRCA1* or *BRCA2*.
- Patients diagnosed between ages 40 and 59 had similar likelihoods of having a mutation in *BRCA1/ BRCA2* or one of the 10 other breast cancerpredisposing genes on the panel.
- Patients diagnosed over the age of 60 were more likely to have a mutation in a gene other than *BRCA1* or *BRCA2*.
- The average age at diagnosis for patients with a *BRCA2* mutation (n=381) was 47, which is nearly identical to patients with mutations in *ATM* (age 49, n=173), *PALB2* (age 48, n=152), and *CHEK2* (age 47, n=189).
- o Only patients who provided age data are included.



CONCLUSIONS

- Testing of patients with a personal history of breast cancer using a 25-gene panel identified 51.1% of mutations in genes other than *BRCA1* and *BRCA2*. This represents an 104.5% increase in mutations identified by single-syndrome testing only.
- 9.0% of patients had a mutation in a gene not associated with breast cancer, but with significant other cancer risks that can now be addressed. This includes genes with a significant colorectal cancer risk (LS genes and APC) that would have been missed in a breast cancer-specific panel.
- 45 patients were found to have more than one mutation, providing the opportunity to appropriately modify medical management for these patients and their family members.