HEREDITARY CANCER TESTING FOR PATIENTS OF ASHKENAZI JEWISH ANCESTRY IN THE ERA OF PANEL TESTING

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HYPOTHESIS / PURPOSE

- Due to the high prevalence of three founder mutations in *BRCA1/2* among individuals of Ashkenazi Jewish (AJ) ancestry, current NCCN guidelines recommend founder mutation testing for all AJ individuals with a personal history, or close relative diagnosed with breast, ovarian, pancreatic, or prostate cancer (Gleason score ≥7) at any age.
- AJ individuals negative for the three founder mutations are candidates for full analysis of *BRCA1/2* if they meet additional criteria. Current data suggests that this results in the identification of additional individuals with pathogenic variants in *BRCA1/2*.
- With the advent of panel testing, we hypothesized that "reflexing" individuals of AJ ancestry to a 25-gene hereditary cancer panel following negative founder mutation testing would substantially increase the number of pathogenic variants identified, compared to *BRCA1/2* testing alone.

METHODS

- We analyzed results from clinical testing of all individuals reporting full or partial AJ ancestry who had reflex testing with a 25-gene hereditary cancer panel after negative results from testing for the three *BRCA1/2* AJ founder mutations.
- The genes included on the panel are *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *APC*, *MUTYH*, *CDKN2A*, *CDK4*, *TP53*, *PTEN*, *STK11*, *CDH1*, *BMPR1A*, *SMAD4*, *PALB2*, *CHEK2*, *ATM*, *NBN*, *BARD1*, *BRIP1*, *RAD51C*, and *RAD51D*.
- Sequencing and large rearrangement analysis is performed for all genes on the panel, except *EPCAM*, for which only large rearrangement analysis is performed.
- Pathogenic variants (PVs) are defined as all variants that receive a laboratory classification of Deleterious or Suspected Deleterious.
- All patient information was obtained by health care provider report on the test requisition forms.

RESULTS

- 3,532 individuals of AJ ancestry underwent genetic testing and 173 (4.9%) tested positive for one of the three *BRCA1/2* founder mutations (*BRCA1* 187delAG, *BRCA1* 5385insC, *BRCA2* 6174delT).
- 2,922 individuals reflexed to the 25-gene panel and 63 (2.2%) were identified as having at least one PV.

TABLE 1. *Distribution of PVs Other than the BRCA1/2 Founder Mutations in Individuals of AJ Ancestry*

Gene	Positive	
	N	%
BRCA1	5	7.7%
BRCA2	8	12.3%
CHEK2	11	16.9%
ATM	8	12.3%
MSH6	5	7.7%
PALB2	4	6.2%
NBN	4	6.2%
RAD51D	4	6.2%
MSH2	3	4.6%
PMS2	3	4.6%
RAD51C	3	4.6%
CDKN2A (p16INK4A)	2	3.1%
BARD1	2	3.1%
MLH1	1	1.5%
APC	1	1.5%
BRIP1	1	1.5%

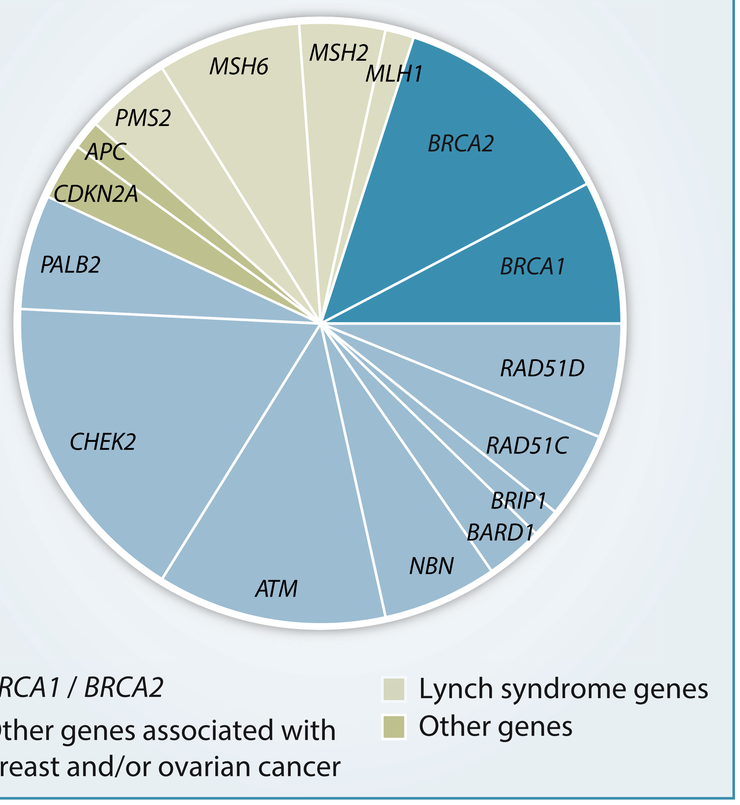
*7 individuals were identified as having a monoallelic *MUTYH* mutation; 179 individuals were identified as having *APC* I1307K.

2 individuals were identified as having 2 PVs, for a total of 65 PVs.

No PVs were identified in the following genes: *BMPR1A*, *CHD1*, *CDK4*, *CDKN2A* (*p14ARF*), *EPCAM*, biallelic *MUTYH*, *PTEN*, *SMAD4*, *STK11*, *TP53*.

- 20.0% (13) of PVs were non-founder PVs in *BRCA1/2* (Table 1).
- 80.0% (52) of PVs were identified in 14 other genes on the panel (Figure 1).
  - This included PVs in *CHEK2* (16.9%), *ATM* (12.3%), and *MSH6* (7.7%).
  - 8/11 PVs in *CHEK2* were the 1100del variant.
- Preliminary analysis suggests that *ATM* c.1027_1030del is a founder mutation in the AJ population.
  - This PV has been observed in three individuals from the full 25-gene panel testing cohort, all of whom reported full Ashkenazi Jewish ancestry.

FIGURE 1. *Distribution of PVs Other than the BRCA1/2 Founder Mutations in Individuals of AJ Ancestry*



CONCLUSIONS

- For AJ individuals in this cohort who tested negative for the three *BRCA1/2* founder mutations, there was a four-fold increase in PVs identified by reflexing to a 25-gene panel rather than *BRCA1/2* testing alone.
- This supports the hypothesis that the yield from multi-gene panel testing is significantly higher compared with comprehensive analysis of *BRCA1/2* alone for individuals of AJ ancestry.
- The increase in individuals of AJ ancestry identified as having clinically actionable PVs via panel testing allows appropriate modifications in medical management to reduce cancer risk.

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