#10514: Double jeopardy? A closer look at cancer histories of individuals with multiple germline pathogenic variants

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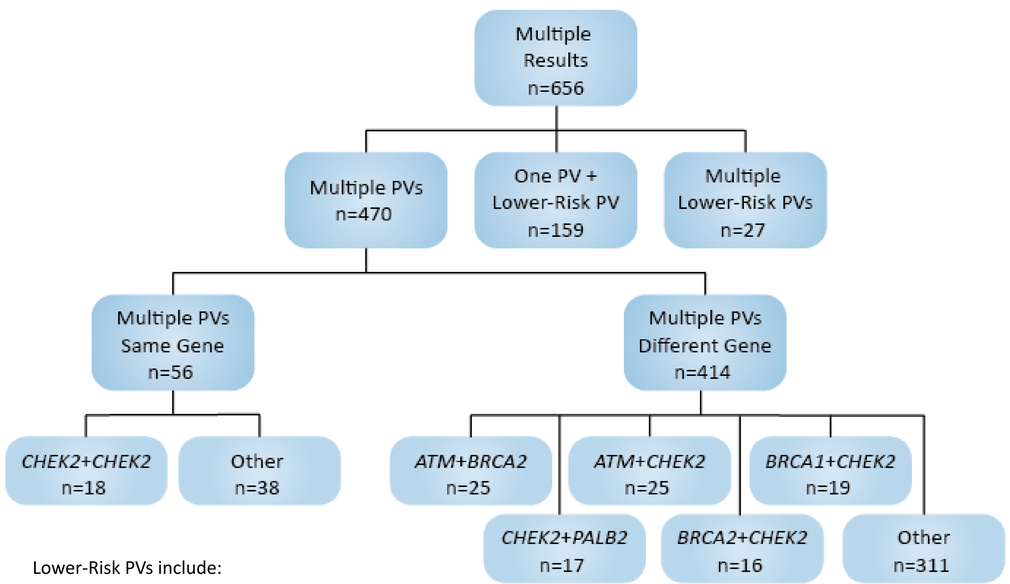
Background and Methods

- Germline multigene panel testing has led to the increased detection of multiple co-occurring pathogenic or likely pathogenic variants (PV) in the same individual.
- Here we describe the clinical features of individuals with multiple PV identified at a single high-volume diagnostic laboratory.
- We performed a retrospective review of demographic and clinical data for individuals with >1 PV who underwent hereditary cancer panel testing (5-67 genes) between May 2012 and April 2017.

Results

Figure 1. Counts of individuals with >1 PV

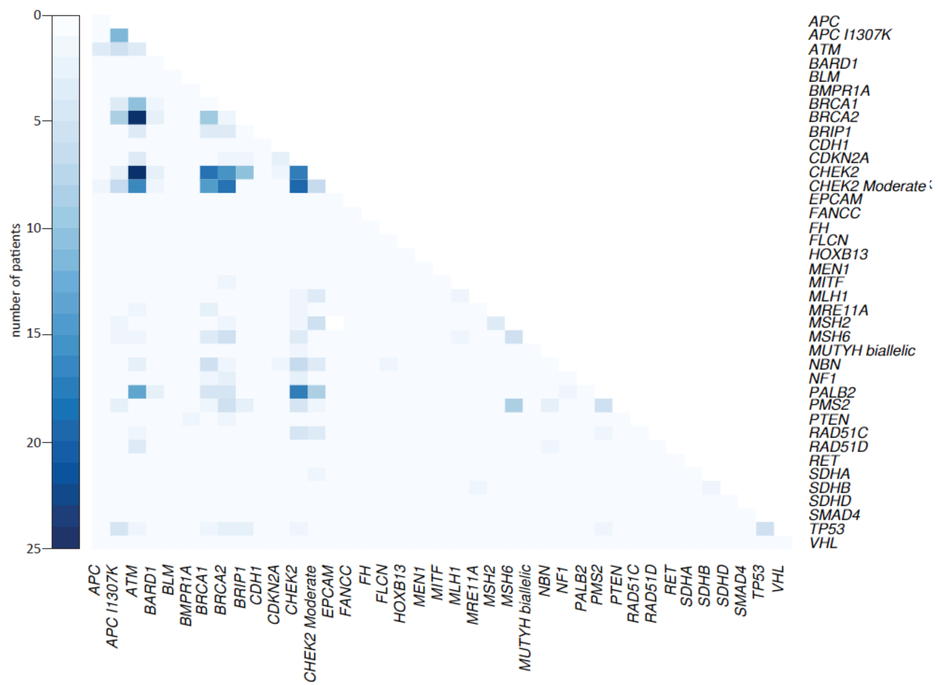


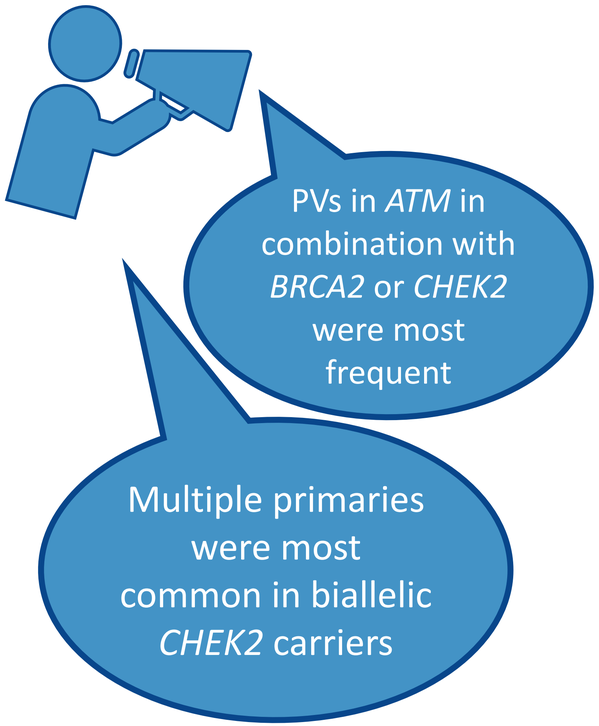
Lower-Risk PVs include:
APC p.I1307K; *CHEK2* p.157T, p.S428F, p.T476M

Table 1. Cancer histories in most frequent co-occurring PV combinations

PV Gene Combination	Total individuals	n Female (%) n Male (%)	Median age 1st cancer (IQR)	n female breast cancer (%*)	n other cancer (%)	n >1 primary cancer (%)
ATM/CHEK2	25	23 (92.0%) *2 (8.0%)*	43 (10.5)	20 (87.0%)	4 (16.0%)	6 (24.0%)
ATM/BRCA2	25	19 (76.0%) *6 (24.0%)*	49.5 (19.5)	11 (57.9%)	9 (36.0%)	5 (20.0%)
BRCA1/CHEK2	19	17 (89.5%) *2 (10.5%)*	44 (10.5)	9 (52.9%)	7 (36.8%)	4 (21.1%)
CHEK2/CHEK2	18	18 (100.0%) *0 (0.0%)*	40 (15)	17 (94.4%)	11 (57.9%)	11 (57.9%)
CHEK2/PALB2	18	18 (100.0%) *0 (0.0%)*	47 (18)	17 (94.4%)	2 (11.1%)	5 (27.8%)
BRCA2/CHEK2	16	15 (93.7%) *1 (6.3%)*	45 (13)	10 (66.7%)	2 (12.5%)	2 (12.5%)

*females only





In Progress

Comparisons of age at breast cancer diagnosis in females with multiple PVs to those with a 1 PV

- No significant difference in age for *BRCA1*+other (*ATM*, *BRCA2*, *CHEK2*, or *PALB2*) or *BRCA2*+other (*ATM*, *CHEK2*, or *PALB2*) compared to single PV
- Females with *ATM*+*CHEK2* had earlier age of breast cancer diagnosis than females with either gene alone

Comparisons of breast cancer hormone receptor status in each concurrent combination