Title: Ashkenazi Jewish descent and panel testing: beyond BRCA founder mutations.

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Objective: The majority of hereditary breast and ovarian cancer syndrome in individuals of Ashkenazi Jewish (AJ) ancestry is attributed to three founder mutations in *BRCA1* and *BRCA2*. Recently, multigene panel testing (MGPT) has allowed testing to expand beyond these genes. The purpose of this study is to determine the frequency of mutations beyond the *BRCA* founders in AJ individuals undergoing MGPT.

Methods: Test results were reviewed for individuals undergoing MGPT from June 2013 to September 2015 at one diagnostic laboratory. Individuals underwent sequencing and deletion/duplication analysis of 5-49 genes. Ethnicity was obtained from requisitions. Statistical analyses were performed using Fisher's exact test.

Results: Of 77,133 individuals undergoing MGPT, 5,143 were AJ. 566 mutations were identified in 541 AJ individuals, yielding an overall positive rate of 10.5%. Of these, 27.9% (N = 158) of mutations were in *BRCA1/2*, 18.4% (N = 29) of which were non-founders. The remaining 72.1% (N = 408) of mutations were in non-*BRCA* genes (N = 131 were moderate risk mutations: *APC* p.I1307K and *CHEK2* p.I157T). Mutations were detected in 28 genes, with *APC*, *CHEK2*, *FH*, and *ATM* most commonly mutated non-*BRCA* genes (7.0%, 3.7%, 1.9%, and 0.9% of individuals tested for each gene, respectively). Interestingly, when comparing across ethnicities, AJ individuals were less likely to test positive for *PALB2* (.3% vs .8%, p = 2.96e-5), but overall, had the highest mutation positive rate in non-*BRCA* genes (7.6% vs 5.4%, p=1.03e-10).

Conclusions: 437 mutations were identified beyond the three founder mutations in *BRCA1* and *BRCA2*, raising the question of when to offer founder mutations vs. MGPT. Prospective cohorts of AJ individuals undergoing MGPT are needed to further assess the prevalence of non-founder mutations. Our results demonstrate that AJ individuals who are candidates for *BRCA1* and *BRCA2* genetic testing are also candidates for MGPT.