TITLE: The impact of high and moderate penetrance breast cancer gene alterations on familial cascade testing in multi-gene panel positive probands

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Single site testing has been the standard of care for familial cascade testing when a proband tests positive for a pathogenic/likely pathogenic (P/LP) variant in a high penetrance breast cancer gene. Here we examined the types of tests ordered for family members of probands that tested positive on a breast cancer multigene panel test (MGPT), and explored the differences in the type of familial testing ordered by healthcare providers if the proband was found to carry an alteration in a high penetrance gene verses a moderate penetrance gene.

Data from probands who tested positive for a P/LP variant on a 17-gene hereditary breast cancer MGPT between August 2012 and December of 2016 were retrospectively reviewed. The ordering trends and results of all subsequent family members tested at a commercial laboratory were assessed. Of the 3187 total probands that received a positive finding on a breast cancer MGPT, 36.7% (N=1534) had at least one family member who received follow up genetic testing while the remaining 63.3% (N=2017) had no subsequent family members tested.

The family members who sent in samples for cascade testing were categorized based on the type of test ordered (Table 1). When a proband was found to carry a P/LP variant, single site testing as follow up for other family members was most common (84.4%); however, some clients chose to order MGPT (13.5%) or single gene testing (2.1%) for family members while referencing the familial alteration in the requisition form. We examined such trends in the types of cascade testing subsequently ordered from 2013 to 2016 in our cohort and observed a steady increase in MGPT ordered for family members of positive probands between 2013 (9.8%) and 2016 (15.5%) and a slight corresponding decrease in single site orders between 2013 (85.9%) and 2016 (82.9%).

We also analyzed the difference in familial ordering patterns based on whether the probands had an alteration in a high penetrance gene (*BRCA1*, *BRCA2*, *CDH1*, *NF1*, *PTEN*, *TP53*) verses a moderate penetrance gene (*ATM, BARD1, BRIP1, CHEK2, MRE11A, MUTYH, NBN, PALB2, RAD50, RAD51C, RAD51D*). Of the 3187 positive probands in our cohort, 1172 (36.8%) had P/LP variants in high penetrance genes only and 1952 (61.2%) had P/LP variants in moderate penetrance genes only. A small proportion had alterations in both high penetrance and moderate penetrance genes and were excluded from the analysis (n=63, 2.0%). Of the 1172 probands with alterations in high penetrance genes only, 1003 family members received familial testing. Of the 1003, 9.0% ordered MGPT, 89.2% ordered single sites, and 1.8% ordered single gene tests. Of the 1952 probands with alterations in moderate penetrance genes only, 1273 family members received familial testing. Of the 1273, 17.0% ordered MGPT, 80.6% ordered single site tests, and 2.4% ordered single gene tests.

Cascade testing continues to be a crucial part of clinical care for families at an increased risk for disease. We show evidence of a slow shift in cascade testing ordering trends with more providers choosing MGPT for family members instead of single site testing to perhaps detect other P/LP variants that could provide a better understanding of the clinical phenotypes seen in a family.

The data also suggest that ordering providers may be more likely to order MGPT for family members when the proband receives a moderate penetrance result.

Table 1

	Test Ordered for Family Member			
Gene Penetrance	MGPT	Single Site	Single Gene	Total
High	90 (9.0%)	895 (89.2%)	18 (1.8%)	1003
Moderate	217 (17.0%)	1026 (80.6%)	30 (2.4%)	1273
Total	307 (13.5%)	1921 (84.4%)	48 (2.1%)	2276