Title: Additional findings amongst relatives pursuing oncology multigene panel cascade testing

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Background Historically, cascade testing performed in family members of probands with a known pathogenic variant (PV) has often been limited to site specific analysis (SSA). Studies investigating outcomes of cascade multigene panel testing (MGPT) as an alternative are limited. This study identified additional familial PVs (AFPVs) and determined if they were unexpected or if positive individuals met testing criteria for the AFVP. This study aims to aid clinicians in determining when cascade MGPT may be more appropriate than SSA.

Methods A retrospective review was performed to identify cascade family members (CFMs) of probands with PVs in *BRCA1/2*, other HBOC genes (*ATM*, *CHEK2*, *PALB2*), and Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*) identified at a single diagnostic laboratory. CFMs were defined as those who had any testing (SSA, single gene, or MGPT) from 2018-2023, after the proband, that included the proband's impacted gene. CFM testing of eight or more genes was considered MGPT. Personal and family history provided by ordering clinicians was reviewed among individuals with an AFPV to evaluate testing criteria eligibility and management recommendations, when available.

Results Of 10,565 total CFMs, 2,953 completed MGPT (27.9%). 222 relatives carried AFPVs (7.5%), with 102 AFPVs in AD genes with medical management guidelines, 94 AFPVs in AR genes, and 12 AFPVs in other genes. AFPVs made up 6.7% of positives among CFMs who had MGPT. AFPVs were most common in relatives of probands with *MLH1* PVs, and AFPVs were most frequently identified within *CHEK2*. Of 102 AFPVs with management guidelines, 78.4% (n=80) had a cancer history consistent with their result, including 66.7% (26 of 39) who met published testing criteria and 85.7% (54 of 63) of those without gene-specific testing criteria. 12 relatives carried AFPVs within the same gene as the proband, which may have been unexpected despite individuals meeting testing criteria.

Conclusion Implementing cascade MGPT increases the overall positive rate, and approximately half of AFPVs are directly tied to medical management recommendations. The majority of relatives with AFPVs impacting medical management had consistent phenotype or met criteria for the AFPV demonstrating the benefit of comprehensive family history collection and pre-test counseling. However, 1 in 5 relatives had an AFPV without suggestive history that would impact their medical management.