

## Increased Detection of Germline Cancer Susceptibility Mutations Subsequent to Tumor Profiling

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**Background:** In addition to guiding targeted therapy, tumor profiling may incidentally reveal germline mutations leading to the diagnosis of hereditary cancer predisposition. When somatic and germline analysis is performed in tandem, 4-13% of patients are found to carry a mutation in a cancer-susceptibility gene. However, the rate of pathogenic mutations is significantly higher (17.5%) when germline testing is performed subsequent to tumor profiling. We sought to examine the frequency and clinical significance of germline testing subsequent to tumor profiling when performed at separate laboratories.

**Methods:** Retrospective review of a laboratory database revealed 175 germline test orders following reported external somatic tumor analysis between June 2014 and April 2017. A description of the patient's tumor, including associated somatic mutations, was obtained from test requisitions. Germline targeted sequencing was performed with DNA isolated from blood or saliva. Pathogenic and likely pathogenic mutations identified in hereditary cancer predisposition genes were included for analysis.

**Results:** Of 175 germline test orders subsequent to molecular tumor profiling, 46 patients (26.3%) were found to carry one or more germline mutation(s) in a hereditary cancer predisposition gene. Of those, 42 (91.3%) of the patients' results were concordant with the somatic mutations detected in their tumor. The remaining 4 patients (2.3% of the total population) had germline mutations detected with no corresponding somatic alteration detected in their tumor.

**Discussion:** The pathogenic mutation rate in this cohort (26.3%) is higher than that typically seen for patients referred for germline testing based on clinical criteria, demonstrating the importance of confirmatory germline testing following tumor profiling. These results also demonstrate the potential for germline testing to identify mutations not indicated by tumor profiling. The detection of pathogenic germline mutations may indicate different medical management guidelines for patients as compared to the finding of somatic tumor profiling alone, and therefore optimal management is achieved when results of both are provided.