

# One of these things is not like the other: clinically actionable discordance between germline sequencing and somatic tumor profiling in cancer patients

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## Background

The analysis of somatic mutations in tumors with next-generation sequencing (NGS) is a rapidly expanding clinical assessment provided to cancer patients, frequently in the absence of dedicated germline testing. A recent study reported that ~13% of patients undergoing somatic tumor mutation profiling (TMP) have a positive result in a known cancer predisposition gene identified in their germline (Schrader, KA, *et al. JAMA Oncol.* 2016; 2(1):104-11). Such findings have potential implications for the acute treatment of patients, ongoing surveillance, and screening of family members. We report a series of patients with positive TMP results who received germline genetic testing, including germline identification rate, cases of discordance between germline and TMP results, and overall potential clinical impact.

## Methods

Our study included de-identified information from 100 consecutive patients who underwent somatic TMP only, had a positive TMP result, and then had germline testing using an NGS-based hereditary cancer gene panel.

## Results

In 64 of 100 (64%) cases, one or more TMP variants in genes associated with hereditary cancer syndromes or genes conferring increased cancer risk were identified somatically but were not observed in the germline test. In 36 of 100 (36%) cases, one or more germline variants were found (Figure 1).

### Germline Origin of Tumor Variants in Cancer Patients

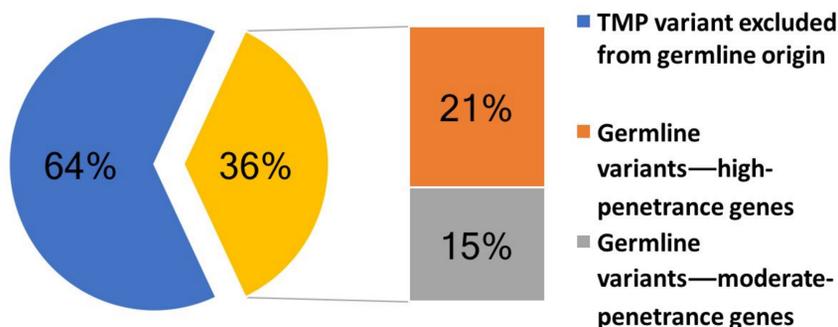


Figure 1. Percent of cases in which the germline origin of a tumor molecular profile (TMP) variant was identified in both high- and moderate-penetrance cancer genes.

Twenty-one were likely pathogenic or pathogenic (LP/P) germline variants found in highly penetrant cancer predisposition genes, and an additional 15 were found in moderate-penetrance genes.

## Results (cont.)

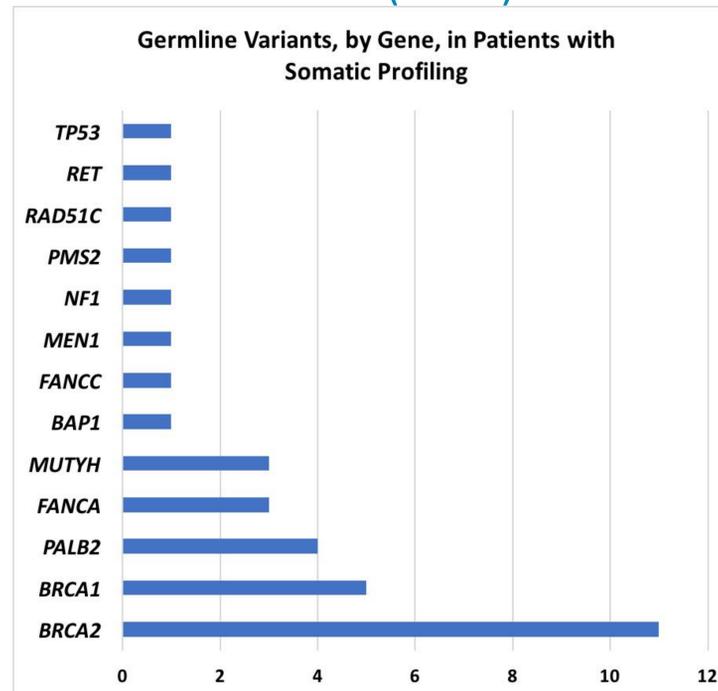


Figure 2. Prevalence, by gene, of pathogenic/likely pathogenic germline variants in patients undergoing somatic tumor molecular profiling (TMP).

The LP/P germline variants identified were in *BRCA2* (11/36), *BRCA1* (5/36), *PALB2* (4/36), *FANCA* (3/36), and *MUTYH* (3/36), with one each confirmed in *BAP1*, *FANCC*, *MEN1*, *NF1*, *PMS2*, *RAD51C*, *RET*, and *TP53* (Figure 2). Of the germline variants identified, 31 were concordant with reported somatic TMP variants.

### Clinically Actionable Findings: Germline vs. Somatic

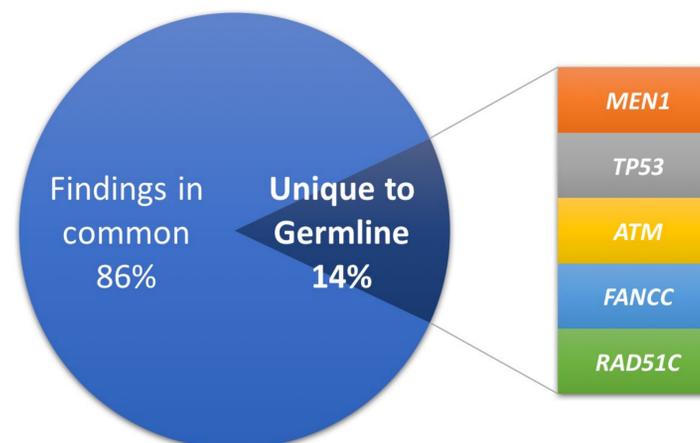


Figure 3. Germline sequencing revealed unique findings, not described in the TMP, for five cases in which the difference was clinically meaningful.

In 5 of 36 cases, the germline variants we identified were discordant with somatic TMP results (Figure 3). In two cases, the discordance was of interpretation—i.e., what was considered a positive somatic TMP variant was interpreted as a variant of uncertain significance in the germline report.

## Results (cont.)

Two of the remaining discordant cases involved *RAD51C* and *FANCC*, in which germline testing identified an LP/P germline variant not reported in the somatic TMP (the genes were not on the TMP panel).

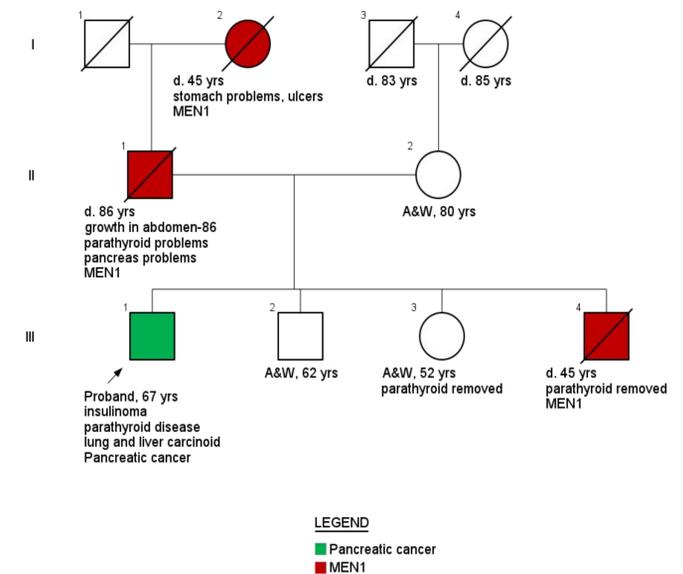


Figure 4. Pedigree of patient with insulinoma and family history of multiple endocrine neoplasia type 1 (MEN1).

The final discordant case was a patient with a neuroendocrine tumor and no *MEN1* mutation on somatic TMP; however, a germline LP/P *MEN1* variant was identified (Figure 4).

## Conclusions

- Thirty-six percent of patients had a somatic TMP variant discovered to be an LP/P germline variant. This high rate may be influenced by clinician selection bias.
- All of the genes in which germline LP/P variants were observed have clinical implications for patients and/or family members.
- Germline testing contributes clinical utility that is not captured by somatic TMP.
- Our results suggest that combining multi-gene panel germline sequencing with somatic TMP may contribute to clinical utility and precision management of patients by
  - Discovering the germline origin of somatic variants
  - Ruling out germline origin of somatic variants in known cancer susceptibility genes
  - Identifying germline variants not reported in somatic TMP results
  - Discovering actionable variants not otherwise indicated for testing by current guidelines