Determining the clinical value of germline genetic testing coupled with tumor mutation profiling

Edward D. Esplin[1], Shan Yang[1], Scott Michalski[1], Karen Ouyang[1], Jennifer Fulbright[1], Barbara Hamlington[1], Karl Erhard[1], Hio Chung Kang[1], Carli Tejada[2], Michelle Jacobs[3], Stephen E. Lincoln[1], Robert L. Nussbaum[1], Amie Blanco[2]
[1]Invitae Corporation, [2]University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, [3]University of Michigan
Contact: Ed.Esplin@Invitae.com

Background

Somatic mutation analysis by next-generation sequencing (NGS) is an expanding clinical assessment offered to cancer patients. Studies report that 4–12% of patients have a positive tumor mutation profiling (TMP) result in a known cancer predisposition gene also identified in their germline, which has potential implications for the patient's acute treatment, ongoing surveillance, and the screening of family members. We report a series of patients with TMP coupled with germline genetic testing and include yield of pathogenic germline mutations, discordance between germline and TMP findings, and potential clinical impact.

Methods

Our study used de-identified data from 100 consecutive patients who underwent TMP followed by germline testing with an NGS-based hereditary cancer gene panel.

Results

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

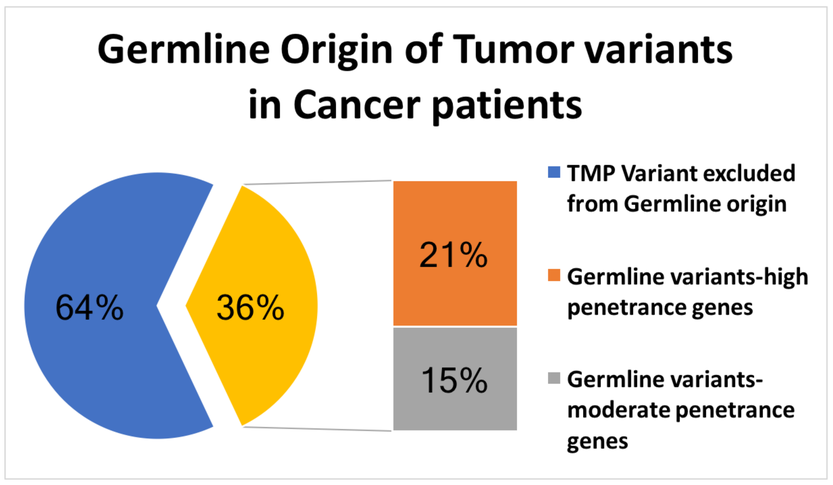

Figure 1. Percent of patient cases where germline origin of a tumor molecular profile (TMP) variant was identified, in both high- and moderate-penetrance cancer genes.

21 were likely pathogenic or pathogenic (LP/P) germline variants found in highly penetrant cancer predisposition genes, and an additional 13 were found in moderate penetrance genes.

Results (cont.)

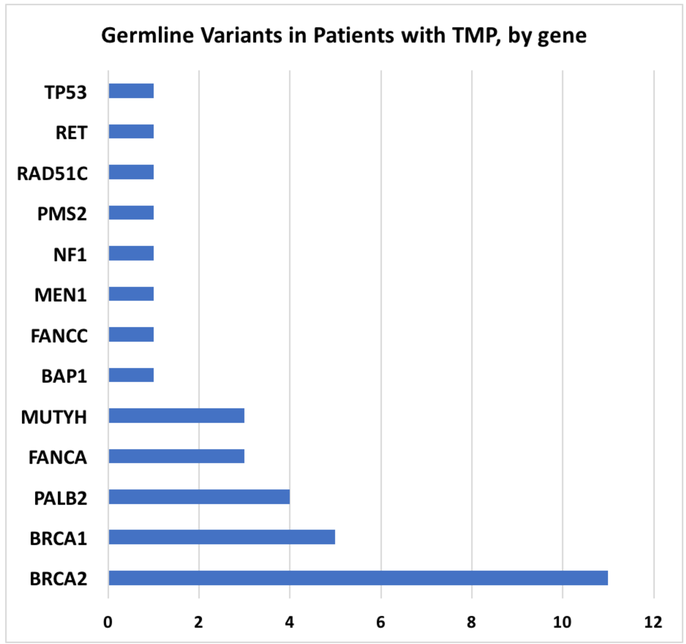

Figure 2. Prevalence, by gene, of pathogenic/likely pathogenic germline variants in patients undergoing tumor moleular profiling (TMP).

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

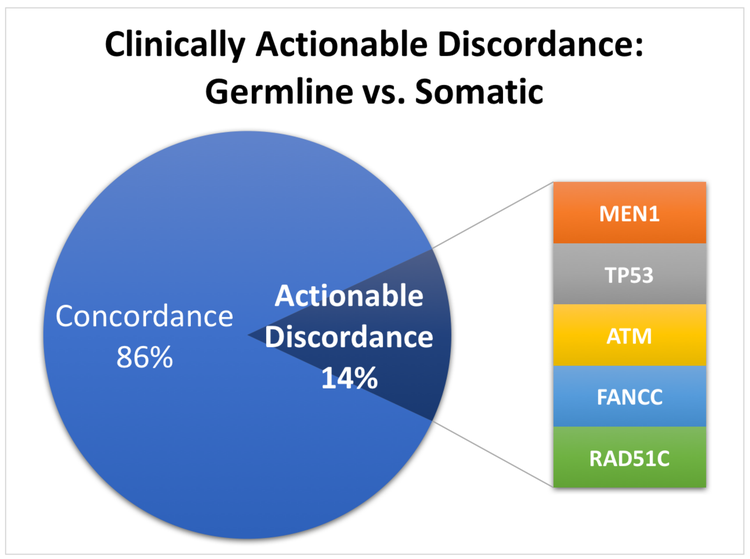

Figure 3. Germline sequencing was discordant with TMP in 5 cases where this was clinically meaningful.

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

Results (cont.)

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

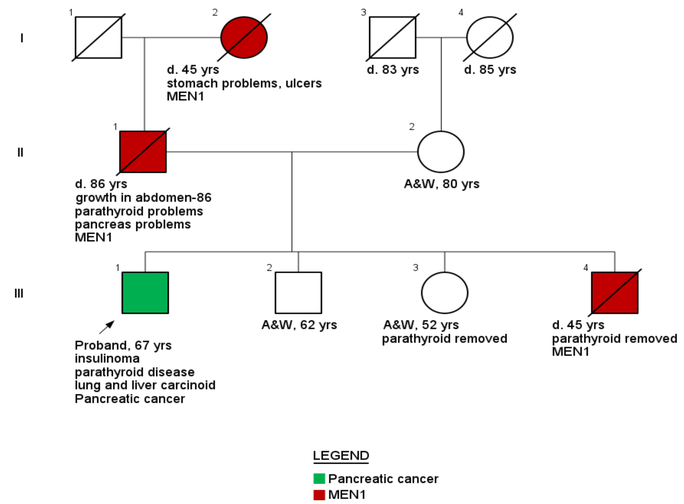

Figure 4. Pedigree of patient with insulinoma and family history of MEN type 1.

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

Conclusions

- In TMP patients, 50 of 182 had a medically actionable germline mutation with established management guidelines. This high rate may be influenced by clinician selection bias. Among these 50, 12 (24%) met neither current personal or family criteria nor the latest NCCN guidelines for germline testing in patients with TMP. Also striking were nine patients whose germline LP/P mutations were absent in TMP results. These data suggest that indications for germline testing of cancer patients must be expanded to avoid missing important germline findings in patients undergoing TMP.

References

[1]Schrader et al. JAMA Oncol. 2016, PMID 26556299