1391- Following Somatic Tumor Testing with Germline Analysis: Considerations for Genetic Counseling Practice

Amie M. Blanco, MS, LCGC
Cancer Genetics and Prevention Program
University of California San Francisco
COI Disclosure

No Conflicts of Interest to Disclose
Background

• Somatic tumor testing (STT) is used to direct targeted therapy and identify candidates for clinical trials

• Studies report that 4-12% of STT findings also occur in the germline

• The application of STT in genetic counseling practice remains undefined
Specific Aims

To investigate the utility of mutation allele frequency (MAF) and existing clinical criteria in directing which patients with STT variants should be offered germline genetic testing.
Methods

- 182 sequential patients sent for germline genetic testing to a single laboratory following STT (multiple STT laboratories)
- Compared STT reports with results of germline genetic testing
- Collected MAF from STT where available
- Compared clinician-reported patient and family history with National Comprehensive Cancer Network (NCCN) genetic testing criteria
Results

182 patients with STT followed by germline genetic testing

- 132 (73%) Negative
  - 50 (27%) Positive P/LP
    - 28 (56%) met criteria for germline testing
    - 12 (24%) did not met criteria
    - 10 (20%) met only BRCA tumor variant criteria

- 50 (27%) Positive P/LP

43 (86%) multi-gene panels
7 (14%) single gene analysis
10 (20%) discrepant results with STT
40 (80%) concordant results with STT
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Results:
Germline origin of tumor variants in cancer patients

- **73%**: STT variant excluded from germline origin
- **27%**: Germline variants: high-penetrance genes
- **18%**: Germline variants: low-penetrance genes
- **9%**: Germline variants: low-penetrance genes
Results:

Germline P/LP variants by gene in patients with STT

- BRCA2
- BRCA1
- PALB2
- MUTYH
- CHEK2
- FANCA
- BAP1
- ATM
- CDKN2A
- FANCC
- MEN1
- MSH2
- NF1
- PMS2
- RAD51C
- RET
- HFE

The graph shows the distribution of germline P/LP variants across these genes, with BRCA2 having the highest frequency.
<table>
<thead>
<tr>
<th>Patient diagnosis</th>
<th>Somatic test result</th>
<th>Germline test result</th>
<th>Reason for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>27 yo F glioblastoma</td>
<td>NF1 R2637*</td>
<td>NF1 duplication (3 copies)</td>
<td>Not reported on somatic test</td>
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<tr>
<td></td>
<td>MSH6 F1088fs*5</td>
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<td></td>
<td>TP53 R273H</td>
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<tr>
<td>60 yo M, pancreatic insulinoma @ 28, metastatic neuroendocrine tumor @ 54</td>
<td>NF1 3113+1G&gt;C</td>
<td>MEN1 c.784-9 G&gt;A (intrinsic)</td>
<td>Not reported on somatic test</td>
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<tr>
<td></td>
<td>NF1 D2095fs*16</td>
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</tr>
<tr>
<td>39 yo F rectal cancer</td>
<td>TP53 E349X</td>
<td>FANCC c.1302dupT</td>
<td>Not reported on somatic test</td>
</tr>
<tr>
<td>50 yo F triple negative breast cancer</td>
<td>SMARCA4 P197S</td>
<td>MUTYH c.1438 G&gt;T</td>
<td>Not reported on somatic test</td>
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<tr>
<td></td>
<td>TP53 R110_L111insL</td>
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<tr>
<td>60 yo M adenocarcinoma of the prostatic urethra</td>
<td>BRCA1 572_S93+23del45</td>
<td>RAD51C c.525dupC</td>
<td>Not on somatic assay</td>
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<tr>
<td>62 yo F leiomyosarcoma, B cell lymphoma, breast cancer</td>
<td>BRCA2 T3033fs*29</td>
<td>CDKN2A c.9_32dup</td>
<td>Not reported on somatic test</td>
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<td></td>
<td>PTCH1 N97fs*43</td>
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<td>TP53 R175H</td>
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<td>TP53 R248Q</td>
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<tr>
<td>42 yo F thyroid cancer</td>
<td>STK11 R331W (c.991C&gt;T)</td>
<td>CHEK2 c.470 T&gt;C (p.Ile157Thr)</td>
<td>STK11 R331W classified at VUS in germline</td>
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<td>CHEK2 c.470T&gt;C not reported on somatic test</td>
</tr>
<tr>
<td>62 yo M bile duct/cholangiocarcinoma at 58 and pancreatic adenocarcinoma at 60</td>
<td>BRCA1 W1718*</td>
<td>BRCA1 c.213-11 T&gt;G (intrinsic)</td>
<td>Not reported on somatic test</td>
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<tr>
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<td>TP53 deletion exons 8-11</td>
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<tr>
<td>53 yo F ovarian cancer</td>
<td>TP53 R282W</td>
<td>HFE c.187 C&gt;G</td>
<td>Not on somatic assay</td>
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<tr>
<td>52 yo F lobular breast cancer at 39, diffuse gastric cancer at 49</td>
<td>TP53 W91*</td>
<td>MUTYH c.1187 G&gt;A</td>
<td>Not reported on somatic test</td>
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<tr>
<td></td>
<td>CDH1 M517fs</td>
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<tr>
<td></td>
<td>RUNX1 R169fs</td>
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Results:

Germline positive patients that met current testing criteria

- Met guidelines for germline testing: 56%
- No guidelines met for germline testing: 24%
- Met NCCN guideline for BRCA1/2 tumor variants: 20%
Results:

Mutation Allele Frequency

• Data available for 10 of 50 patients

• Ranged between 37% and 77%
Discussion

• Germline testing identified a higher yield of P/LP variants than previously reported
• Relevant variants were found in 17 genes, suggesting a role for expanded germline panel testing rather than single gene testing based on STT
• STT may miss germline P/LP variants:
  – Technology (intronic coverage, small in-dels, other structural variants)
  – Variant classification
  – Absence of important cancer predisposition genes on STT
Conclusion

• The range of MAF confirms prior claims that it is not specific for predicting germline variants

• Current guidelines for germline testing must become more inclusive of STT results
  – Cascade genetic testing recommended for families that may not have received genetic counseling and testing otherwise.
Our Collaborators

Amie Blanco, Carli Tejada

Michelle Jacobs

Heather Hampel


Cindy Benson, Lauren Massingham

Cathryn Koptiuch

Hetal Vig

Erica Silver