Germline multigene panel testing in colorectal cancer: Precision therapy and clinical management implications.

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BACKGROUND
- Recent studies suggest that the prevalence of abnormalities in homologous recombination deficiency (HRD) genes and other cancer genes not traditionally associated with colorectal cancer (CRC) may be more common in patients with CRC than previously appreciated.
- Herein, we investigate the efficacy of comprehensive multigene panels in patients with CRC to identify candidates for precision therapies.

METHODS
- A retrospective study was performed on DNA sequencing and exon-level copy number analysis using a next generation sequencing–based hereditary cancer panel in a convenience sample of 9669 consecutive patients (pts) referred for personal history of colon cancer between 2013 and 2018 at a commercial diagnostic laboratory.
- The genes queried varied but consistently included 14 genes on a hereditary CRC panel: the patient data were de-identified and further analyzed for all 83 genes on a large hereditary cancer syndrome panel under an IRB-approved protocol.
- Individuals undergoing testing and test ordered were as selected by the ordering clinician. Clinical information was collected and reviewed for test requisition forms and medical records when provided.

RESULTS

- When restricted to the five Lynch syndrome (LS) genes (MLH1, MSH2, MSH6, PMS2, EPCAM), only 9% of patients had a PILOT finding, which increased to 15% of patients when 19 guidelines-based CRC genes were assessed, and increased to 21% when a comprehensive 83 gene panel was applied.

<table>
<thead>
<tr>
<th>Multigene panel</th>
<th>Positive patients</th>
<th>Percent positive</th>
<th>Percent positive (no recessive, e.g. MUTYH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-genes (Lynch syndrome)</td>
<td>938</td>
<td>9.7%</td>
<td>8.7%</td>
</tr>
<tr>
<td>19-genes</td>
<td>1496</td>
<td>15%</td>
<td>13%</td>
</tr>
<tr>
<td>83-genes</td>
<td>2101</td>
<td>21%</td>
<td>19%</td>
</tr>
<tr>
<td>Total patients</td>
<td>9669</td>
<td></td>
<td></td>
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</tbody>
</table>

Table 1: Finding rate of passenger/likely passenger (PILOT) mutations using different multigene panels in patients with colorectal cancer (CRC).

RESULTS (cont.)

- When a comprehensive mutigene panel was utilized, germline PILOT variants in genes with known therapeutic implications, such as in HRD and mismatch repair deficiency (MMRD), were detected in 1408 (14%) of patients, and 1670 (17%) had PILOT variants in genes with established clinical management guidelines.

CONCLUSIONS
- This study suggests that 1 in 5 patients with CRC referred for genetic testing harbor actionable germline mutations.
- Up to one-half of germline mutations remain undetected when only Lynch Syndrome genes are tested.
- Comprehensive germline testing revealed precision therapy eligibility (e.g. HRD, MMRD) for 1,408 (15%) patients.