Common Attributes in Mutation Carriers Identified in a 32-Gene Hereditary Cancer Panel

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BACKGROUND
- The use of multi-gene panel testing (MGPT) with next generation sequencing (NGS) to detect hereditary cancer syndromes has become increasingly common in the United States.
- MGPT has identified more individuals with increased cancer risk than traditional methods, including mutations in genes that were not suspected and in patients with cancers not routinely considered for genetic testing.
- Which patients should have MGPT and what results may be found are common questions among clinicians, and the likelihood of finding a mutation is heavily considered in determining who should have testing.
- Our study aims to assess and compare the mutation frequencies among patients on CancerNext™, an NGS panel of 22-32 genes during the time studied.

METHODS
De-identified clinical and demographic data from 11,363 consecutive cases submitted to Ambry Genetics for CancerNext testing between March 2012 and June 2015 were retrospectively reviewed. Mutation rates and ages at diagnosis were compared for 9 cancer types using logistic regression analysis, controlling for other cancer diagnoses.

We examined the following:
- Significance of age at diagnosis and tumor type in identifying a mutation
- Positive rates in affected patients compared to unaffected patients
- Positive rates found on MGPT in comparison to positive rates within the same test for the most commonly ordered single syndrome test by tumor type

TABLE 1A/B: Demographics

<table>
<thead>
<tr>
<th>Age at first cancer diagnosis</th>
<th>Mean &amp; SD (range) or numbers (%)</th>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
<th>Mean &amp; SD (range) or numbers (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at testing</td>
<td>54.7 ± 12.9 (2.8, 97.5)</td>
<td></td>
<td></td>
<td></td>
<td>48.4 ± 12.6 (0.8, 93)</td>
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</tbody>
</table>

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<thead>
<tr>
<th>Ethnicity</th>
<th>Mean &amp; SD (range) or numbers (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>6838/161688 (58.4%)</td>
</tr>
<tr>
<td>Unknown/Other</td>
<td>2856/161688 (24.4%)</td>
</tr>
<tr>
<td>African American</td>
<td>489/161688 (4.2%)</td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td>431/161688 (3.7%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>406/161688 (3.5%)</td>
</tr>
<tr>
<td>Asian</td>
<td>238/161688 (2.0%)</td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td>112/161688 (1.0%)</td>
</tr>
<tr>
<td>Mixed Caucasian &amp; Other</td>
<td>328/161688 (2.8%)</td>
</tr>
</tbody>
</table>

TABLE 2: Younger ages of diagnosis were associated with higher mutation rates in brain (p = 0.03), ovarian (p=0.02) and breast cancer (p = 0.0002). Table 3: Except for thyroid and gastric carcinoma, all cancer diagnoses were significantly more likely to yield a positive result than in an unaffcted patient (Table 3).

Figure 1: Testing for genes other than BRCA1/2 and Lynch syndrome has the potential to dramatically increase the positive rates with patients of wider age ranges than previously thought.

TAKE-HOME POINTS
- Patients diagnosed with cancer had a higher detection rate, showing the utility of testing an affected individual whenever possible.
- Age of diagnosis only had a significant effect on positive rate in a few cancer types, which may suggest genetic testing in patients of wider age ranges than previously thought.
- The gene-specific breakdown supports previous studies on MGPT in commonly studied cancer types and highlights interesting new associations for brain, sarcoma, and thyroid cancer. CHEK2 mutations were frequent amongst many cancer types, demonstrating the high frequency of mutations in this gene, but it remains unclear what cancer types CHEK2 mutations increase the risk to develop.
- Panel testing significantly increases the rate of mutation detection.
- Additional work is needed to further delineate which factors impact CancerNext detection rates and by how much.

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