An Opportunity or Dilemma? Customizable Panel Tests and Clinician Ordering Behavior
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Introduction
Inherent in the concept of precision medicine is the customization of therapies and associated diagnostic testing. Multi-gene genetic tests have become increasingly available, but the pre-curated gene panels selected by laboratories may or may not always provide the exact information desired by a clinician or patient. Our laboratory offers both customized and a variety of pre-curated panels at a single price regardless of the number of genes ordered. In this study we sought to understand clinician preferences for theses different genetic tests in the setting of hereditary cancer risk assessment.

Materials and Methods
Our laboratory offers both custom and pre-curated germline panels at a single price regardless of the number of genes ordered. The pre-curated panels (as of April 2015) include:

- Inherently moderate-risk hereditary cancers
- High-risk hereditary breast cancer
- Inherently high-risk hereditary colorectal cancer
- Inherently high-risk hereditary ovarian cancer
- Inherently high-risk hereditary pancreatic cancer
- Women’s hereditary cancers
- Hereditary cancer syndromes

Customization of Panels By Ordering Clinician

More than half of clinicians ordered customized tests, at least sometimes. We examined the behavior of high-volume (HV) vs. lower volume (LV) ordering clinicians and found that:
- HV clinicians tend to order pre-curated panels slightly more frequently than LV clinicians.
- The majority of HV clinicians vary test orders, but not all.

Panel Choice By Indication

<table>
<thead>
<tr>
<th>Indication</th>
<th>Pre-curated</th>
<th>Customized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Ca</td>
<td>54.3%</td>
<td>45.7%</td>
</tr>
<tr>
<td>Ovarian Ca</td>
<td>65.1%</td>
<td>34.9%</td>
</tr>
<tr>
<td>Colon Ca</td>
<td>63.9%</td>
<td>36.1%</td>
</tr>
</tbody>
</table>

Panel customization varied by indication for testing, with Ovarian and Colon tests more often using a pre-defined panel compared with Breast. Colon tests were more likely to include the full hereditary cancer gene set, which includes genes not currently known to be strongly associated with Colon cancer.

Results (cont.)

The Hereditary Cancer Syndromes Panel* (29 genes, a large panel) and the high-risk hereditary breast cancer (7 genes, a small panel) were the most common tests ordered.

Results (cont.)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Primary Factor</th>
<th>Secondary Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal/Family History</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Patient Preference/Comfort</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Clinical Utility of Genes on the Panel</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Insurance Coverage</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>-</td>
</tr>
</tbody>
</table>

Customized panel orders 2-118. See invitae.com for details.

Table 1. Hereditary cancer related panels offered by Invitae during the time this study was performed. See invitae.com for details and current panels offered.

To initially assess the behavior of healthcare providers in a scenario where neither cost nor turn around time vary by the number of genes ordered, we selected 183 clinicians who had placed at least 2 orders for patients with a hereditary cancer indication between January and November 2014. Orders from each clinician were categorized to reflect trends including breadth of orders (number of genes), degree of order customization, and ordering consistency across patients.

Interviews
To investigate the rationale underlying the ordering patterns observed, we identified providers who ordered multiple panel tests and invited them to participate in a brief interview. To date we have received detailed responses from 14. Five general topics guided the roughly 10 minute interview:
- Do you order more pre-curated or customized panels?
- What primary factors guide your choice of panel?
- Do you tend toward larger or smaller panels?
- How does patient preference influence panel selection?
- What utility do you find in customizing panels?

Results
1743 tests with an indication of personal or family history of cancer were ordered by these 183 clinicians (on average, 9.5 tests per clinician). Most test orders were for pre-curated panels (53%), averaging 24 genes per test, although many ordering clinicians customized panels, at least sometimes. Over a third of all orders (37%) were for the Hereditary-Cancer Syndromes panel (29 genes)*. Customized tests had a smaller average of 10 genes per test. Roughly half of clinicians had consistent ordering patterns, while the others varied their orders more frequently. Tests for hereditary breast cancer were more likely to be customized by contrast with those for ovarian or colon cancer.

Conclusions
We observed a significant diversity of ordering behaviors for hereditary-cancer panels ordered both between clinicians and by individual clinicians. This included a tendency toward larger pre-curated gene panels, with a sizable minority (13%) of the orders being fully customized based on the available panels. Factors the clinicians indicated influence their selection included clinical indications, patient preference and characteristics of the offered panels, such as clinical utility of genes on the panel and insurance coverage. There is a desire within the genetics community to understand practices in the rapidly changing area of genetic testing. To help answer these questions more extensive studies of provider ordering behavior and rationale will be highly valuable.

Acknowledgements
We gratefully thank the clinicians who took the time to speak with us in this interview process. Special thanks go to Lucy Mower and Katie Riklin for helping us retrieve test order data for this project.

*The same panel contains 34 genes as of Nov. 2015.