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 genes 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, and we sought to understand clinician preferences for these genetic tests in the setting of hereditary cancer.

Most test orders were for pre-curated panels, averaging 24 genes per test, although many ordering clinicians customized panels, at least sometimes. Customized tests had a smaller average of 10 genes per test. Over a third of orders were for the full hereditary-cancer panel (29 genes). 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.

Preliminary interviews with providers suggest that various factors contribute to these patterns, including specific clinical presentation, ordering convenience, patient preference, and other factors.

### Study Design

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 include the following:

<table>
<thead>
<tr>
<th>Panels</th>
<th>N</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast cancer, moderate-risk panel</td>
<td>5</td>
<td>ATM, BRIP1, CHEK2, NBN, RAD51C</td>
</tr>
<tr>
<td>Hereditary breast cancer, high-risk panel</td>
<td>7</td>
<td>BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11, TP53</td>
</tr>
<tr>
<td>Hereditary colon cancer, high-risk panel</td>
<td>7</td>
<td>APC, EPCAM, MSH2, MSH6, MUTYH, PM2</td>
</tr>
<tr>
<td>Hereditary breast cancer, extended panel</td>
<td>12</td>
<td>ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, NBN, PALB2, PTEN, RAD51C, STK11, TP53</td>
</tr>
<tr>
<td>Hereditary colon cancer</td>
<td>14</td>
<td>APC, BMP3, CDH1, CHEK2, EPCAM, MSH2, MSH6, MUTYH, PM2, PTEN, SMAD4, STK11, TP53</td>
</tr>
<tr>
<td>Hereditary pancreatic cancer</td>
<td>17</td>
<td>ATM, BRCA1, BRCA2, CDH1, CHEK2, EPCAM, FANCC, MEN1, MSH2, MSH6, NBN, PALB2, PALP1, PTEN, RAD51C, STK11, TP53</td>
</tr>
<tr>
<td>Women's hereditary cancers</td>
<td>17</td>
<td>ATM, BRCA1, BRCA2, BRIP1, CHEK2, CDH1, EPCAM, MSH2, MSH6, NBN, PALB2, PALP1, PTEN, RAD51C, SMAD4, STK11, TP53</td>
</tr>
<tr>
<td>Hereditary cancer syndromes</td>
<td>29</td>
<td>APC, ATM, BMP3, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, CDH1, CHEK2, EPCAM, MSH2, MSH6, NBN, PALB2, PALP1, PTEN, RAD51C, RET, SMAD4, STK11, TP53</td>
</tr>
<tr>
<td>Customized panel</td>
<td>1-216</td>
<td>See Invitae.com for details</td>
</tr>
</tbody>
</table>

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.

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 customization of orders, and ordering consistency across patients.

### Interviews

To investigate the rationale underlying the ordering patterns observed, we identified providers who ordered multiple panel tests for a hereditary-cancer indication and invited them via email to participate in a brief interview. To date, we have reached out to 25 providers, and we received detailed responses from 13. 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?

### 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, but not all, vary test orders.

When test orders are customized, most commonly this is done by removing genes from a panel. Less commonly, genes are added or a fully custom panel is defined by the clinician.

### Panel Choice by Indication

Panel customization varied by indication for testing, with ovarian cancer and colon cancer tests more often using a pre-defined panel by comparison with breast cancer. Colon cancer 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.

### Provider Responses

Among the respondents, 75% ordered primarily pre-curated panels. Also, 75% (but not the same list of respondents) reported to us that their guiding principle was to order the maximum number of potentially relevant genes.

### Summary

We observed a significant diversity of ordering behaviors for hereditary-cancer panels both between clinicians and by individuals. This included a tendency toward larger pre-curated gene panels, with a sizable minority choosing to customize 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.

### Acknowledgments

We gratefully thank the clinicians who took the time to speak with us in this interview process. Special thanks goes to Lacy Morrow and Katie Riklin for helping us retrieve test-order data for this project.