Carrier Screening: Should Evaluating More Genes Be the Standard of Care?

To report ordering patterns within and outside of ACOG carrier screening guidelines.

For over five years, our laboratory has offered diagnostic testing for >1,000 genes, including high impact disorders, disorders that are well understood, severe, and have a carrier frequency of 1/100 or greater.2,4

Over an eight-month period, 12,688 patient samples were tested. Orders came from 1,049 unique clinicians (20% REI, 21% ObGyn, 12% GCs, 9% MFM, and 39% Other). Half of all orders came from REIs. ACOG acknowledges that expanded carrier screening (ECS) has many benefits but advises that expanded panels should only include high impact disorders, that are well-understood, severe, and have a carrier frequency of 1/100 or greater.2,4

Pre-set panels (available with or without X-linked disorders) include:
- Core Panel (including CF, SMA, and fragile X syndrome)
- Broad Panel (including 46 high-impact genes)
- Comprehensive Panel (including 288 genes)
- Add-on genes (including 13 genes that can lead to variable clinical presentation (e.g., factor V Leiden (F5)) are available as an add-on to any panel

Table 1. Ordering Patterns and Positive Rates

<table>
<thead>
<tr>
<th>Panel</th>
<th># of Genes</th>
<th>% Positive rate</th>
<th>% Concurrent</th>
<th>% of all orders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comprehensive Panel with all Add-On genes (All genes)</td>
<td>301</td>
<td>77%</td>
<td>69%</td>
<td>15%</td>
</tr>
<tr>
<td>Comprehensive Panel</td>
<td>288</td>
<td>65%</td>
<td>68%</td>
<td>40%</td>
</tr>
<tr>
<td>Core Panel</td>
<td>46</td>
<td>44%</td>
<td>44%</td>
<td>13%</td>
</tr>
<tr>
<td>Other: ACOG/ACMG ethnicity-specific genes</td>
<td>4-24</td>
<td>22%</td>
<td>23%</td>
<td>10%</td>
</tr>
<tr>
<td>Other: All other combinations</td>
<td>1-300</td>
<td>varies</td>
<td>62%</td>
<td>7%</td>
</tr>
<tr>
<td>Total</td>
<td>1-301</td>
<td>51%</td>
<td>61%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Results:

Over an eight-month period, 12,688 patient samples were tested. Orders came from 1,049 unique clinicians (20% REI, 21% ObGyn, 12% GCs, 9% MFM, and 39% Other). Half of all orders came from REIs. ACOG acknowledges that expanded carrier screening (ECS) has many benefits but advises that expanded panels should only include high impact disorders, that are well-understood, severe, and have a carrier frequency of 1/100 or greater.2,4

The largest pre-curated panel (288 genes) was ordered most frequently (n=1,821), followed by the Core Panel (n=1,868), all genes (n=1,865), and the Broad Panel (n=1,668). The remaining 2,116 orders were for variable combinations of genes. As expected, the positive rate increased with the number of genes tested (Table 1).

Of 2,151 opposite-sex couple orders we are aware of, 61% were sent concurrently and 39% took a tiered approach, only testing the partner when the patient was positive. When filtered for pregnant couples, 69% ordered concurrently.

Three, 4, and 8 disorders were positive for 3, 4, and 8 disorders, respectively. The most common autosomal recessive disorders at-risk couples screened for (add-on genes excluded) include CFT-related disorders, HBB-related hemoglobinopathies, phenylalanine hydroxylase deficiency (PKU), and GJB2-related non-syndromic hearing loss, Smith-Lemli-Opitz syndrome, Gaucher disease and SMA.

Objective: To report ordering patterns within and outside of ACOG carrier screening guidelines.

Methods: Testing was run for up to 301 genes in different combinations. Testing was performed by next-generation sequencing with deletion and duplication analysis.

Real-time variant interpretation was performed and pathogenic and likely pathogenic variants were reported. Ordering patterns and positive rates were assessed.

Figure 1. Orders by Clinician Type

CONCLUSIONS

Despite current ACOG criteria, our data suggests that when given a choice, 55% of clinicians order a large panel (>288 genes), even including frequent/variable disorders; however, 25% still follow a conservative pan-European or ethnicity-specific approach.

Additional information is needed to understand the decision tree within and between practices including the role insurance coverage and cost plays on carrier screening ordering.

Results:

The most common autosomal recessive disorders at-risk couples screened positive for (add-on genes excluded) include CFT-related disorders, HBB-related hemoglobinopathies, phenylalanine hydroxylase deficiency (PKU), and GJB2-related non-syndromic hearing loss, Smith-Lemli-Opitz syndrome, Gaucher disease and SMA.

Of note, at-risk couples pursued preimplantation genetic diagnosis (PGT-M) for disorders on all pre-curated panels. Approximately 25% of couples known to pursue PGT-M did so for disorders outside of ACOG / ACMG guidelines, indicating that patients use the information from expanded carrier screening to make reproductive healthcare decisions.

Disclosure: All authors are employees and stockholders of Invitae.

References:

Dana Neitzel, Susan Glass, Jocelyn Leahy, Nicole Faulkner
Invitae, San Francisco, CA