Limitations of HBOC direct-to-consumer genetic screening: False positives, false negatives and everything in between

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Financial Disclosure

Nothing to disclose
The FDA authorized a direct-to-consumer (DTC) screen to report on the 3 Ashkenazi Jewish (AJ) founder variants in BRCA1/BRCA2

- “The test only detects three out of more than 1,000 known BRCA mutations.”
- “…negative result does not rule out…an individual carries…BRCA mutations…”
- “…should not use test results to determine any treatments…such decisions require confirmatory testing”
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False Negative=False Reassurance

False Positive=Unnecessary treatment
Methods

• Analyzed de-identified data from three cohorts:
  – Indication-based cohort of 119,328 patients referred for personal or family history of HBOC-related cancer
  – Screening cohort of 5,170 individuals without personal or family history who had BRCA1/BRCA2 testing as a health screen
  – Confirmation cohort of 102 individuals referred for clinician confirmation of positive DTC results
Overall Positive Rate in Patients Referred for HBOC Genetic Testing

![Pie chart showing positive and negative rates for HBOC genetic testing.]

12,846, 11%
106,482, 89%

- Positive for P/LP variant in any HCS-associated gene
- Negative for P/LP variants

Figure 1. Positive rate of hereditary cancer susceptibility genetic testing in referred patients. P/LP – pathogenic/likely pathogenic, HCS – hereditary cancer susceptibility.
AJ founder mutations in patients with an indication for BRCA1/2 testing

Figure 2. Fraction of AJ founder mutations among patients with a clinical indication for HBOC genetic testing. AJ founder mutation – Ashkenazi Jewish founder mutations including c.68_69delAG (BRCA1), c.5266dupC (BRCA1), c.5946delT (BRCA2).
<table>
<thead>
<tr>
<th>Patient self-declared ethnicity</th>
<th>Total tested</th>
<th>P/LP mutations in any HCS gene</th>
<th>BRCA1/2 P/LP mutations among all P/LP mutations in HCS genes (% Total with P/LP mutation)</th>
<th>BRCA1/2 P/LP that are not AJ founder mutations (% of all BRCA1/BRCA2 mutations)</th>
<th>BRCA1/2 P/LP due to 3 AJ founder mutations (% of all BRCA1/BRCA2 mutations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-AJ</td>
<td>112,681</td>
<td>12,298 (10.9%)</td>
<td>4,346 (35.3%)</td>
<td>4,087 (94%)</td>
<td>259† (6%)</td>
</tr>
<tr>
<td>AJ</td>
<td>6,647</td>
<td>791 (11.9%)</td>
<td>387 (49%)</td>
<td>73 (19%)</td>
<td>315‡ (81%)</td>
</tr>
<tr>
<td>Total</td>
<td>119,328</td>
<td>13,089 (11%)</td>
<td>4,733 (36%)</td>
<td>4,160 (88%)</td>
<td>574 (12%)</td>
</tr>
</tbody>
</table>

Table 1. Pathogenic/Likely Pathogenic (P/LP) Mutations in Hereditary Cancer Syndrome Genes in 119,328 Patients Referred for HBOC Gene Testing Due to Personal or Family History of Breast or Ovarian Cancer

†Includes 99/259 (38%) c.68_69delAG (BRCA1), 115/259 (44%) c.5266dupC (BRCA1), and 47/259 (18%) c.5946delT (BRCA2).
‡Includes 117/315 (37%) c.68_69delAG (BRCA1), 38/315 (12%) c.5266dupC (BRCA1), and 160/315 (51%) c.5946delT (BRCA2).
False Negative rate – Healthy screening cohort

AJ founder mutations in healthy individuals

- 12% AJ founder mutations in BRCA1/2
- 88% BRCA1/2 P/LP variants

Clinical false-negative rate
Figure 4. Total number of patients with DTC screening results that underwent confirmation via clinical genetic testing, and the number of patients whose results were found to be analytic false-positives.
Conclusions

• DTC screening restricted to the Ashkenazi Jewish founder mutations in BRCA1/2 has significant limitations

• Despite warnings from the FDA\(^1\), these limitations may not be well understood, lead to false reassurance and DTC genetic screening should be used with caution

• We observed 19% of Ashkenazi Jewish patients carry a non-founder BRCA1/2 mutation, which is higher than previously reported\(^2\)

• Hereditary cancer susceptibility genetic screening should include the support of a qualified clinician to assess limitations and implement appropriate clinical management for patients and their family members
“test results…require confirmatory testing”

Positive DTC result

Clinical Genetic Testing

Negative DTC result

“…negative test result could still mean…risk of cancer due to gene mutations”
References

1. Food and Drug Administration, https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm599560.htm

Acknowledgements

- Eden Haverfield, PhD, FACMG
- Shan Yang, PhD
- Blanca Herrera, PhD
- Michael J. Anderson, PhD
- Robert L. Nussbaum, MD, FACMG, FACP
- Nadine Tung, MD
- Claudine Isaacs, MD
- Erin Hoffstetter, MD
Appendix
Everything in between...

AJ Founder mutations vs all HCS P/LP variants

4.40%

95.60%

Clinical false-negative rate
Case example

“Yes, great news!
Case example

“Yes, great news!

My son is negative, and since he has 3 daughters we are very relieved.
Case example

“Yes, great news! My son is negative, and since he has 3 daughters we are very relieved. Good thing [DTC] is so easy to get!”
Case example

“Yes, great news!

My son is negative, and since he has 3 daughters we are very relieved.

Good thing [DTC] is so easy to get!”

This should NEVER happen!
Acknowledgements

IN V I T A E

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Add your presentation between Financial Disclosure and Acknowledgements slides