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

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Background

Genetic screening of unaffected individuals for hereditary breast and ovarian cancer (HBOC) risk is a growing opportunity for personalized preventive medicine. The FDA recently authorized a direct-to-consumer (DTC) test to report on 3 BRCA1/2 founder mutations, commonly found in individuals of Ashkenazi Jewish (AJ) heritage, out of more than 1000 known. Here we define the probability that DTC genetic screening for the 3 BRCA1/2 AJ founder variants would falsely reassure individuals of AJ and non-AJ ancestry of low risk for hereditary cancer syndromes (HCS). We also assess the frequency of false positive results identified by third parties from raw genotypes, which are routinely provided to clients who submit them for cancer risk analysis.

Methods

We analyzed, per an IRB approved protocol, de-identified data on three cohorts: 1) An indication-based cohort of 119,328 patients referred by healthcare providers for HBOC genetic testing due to personal or family history, or 2) a screening cohort of 5,170 patients without personal or family history who had BRCA1/2 testing as a health screen, and 3) a confirmation cohort of 102 referred for confirmatory confirmatory testing by mail from positive DTC results from third party analysis of raw data.

Results

Overall Positive Rate in Patients Referred for HBOC Genetic Testing: 12,846, 11%

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

Negative for P/LP variants

Clinical false-negative rate for patients with test indication

In the indication-based cohort 12,846 patients had a mutation in any HCS-associated gene (Fig. 1). AJ founder mutation rate was 12% among all BRCA1/2 positive patients with an indication for testing (Fig. 2). Ethnicity impacted AJ founder frequency: 81% of AJ patients with any BRCA1/2 mutation had one of the 3 founder mutations, but only 6% of non-AJ patients (Table 1). Overall clinical false-negative rate for the 3 AJ founder mutations in BRCA2/2 carriers was 88%, rates were 19% and 94% among AJ and non-AJ individuals, respectively (Table 1).

Clinical false-negative rate for ostensibly healthy individuals

Our screening cohort was comprised of ostensibly healthy individuals as might be expected to participate in direct-to-consumer genetic screening. In this screening cohort, where 2.6% were AJ, 40 patients had a P/LP mutation in BRCA1/2. 12.5% were an AJ founder mutation. The clinical false-negative rate of 88.5% for any BRCA2 mutations in the screening cohort is similar to the indication-based cohort (Fig. 3).

Analytic false-positive rate for DTC screening

The confirmation cohort consisted of patients who underwent DTC screening, and in some cases was supplemented by third party raw data analysis. In this confirmation cohort, among patients told of a positive DTC screening result, our analysis indicated 50% (57/115) were analytic false positives (Fig. 4).

Conclusions

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

• Clinical false-negative rates were 19% and 94% among AJ and non-AJ individuals, respectively.

• Despite warnings from the FDA, these limitations may not be well understood 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.

• Patients screened for HBOC on a platform limited to the AJ founder variants should receive confirmatory clinical genetic testing, regardless of having either a positive or negative result.

• These results suggest that all 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.

References:

Figure 1. Positive rate of hereditary cancer susceptibility genetic testing in referred patients. P/LP = pathogenic/likely pathogenic, HCS = hereditary cancer susceptibility

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).

Figure 3. Clinical false-negative rate in ostensibly healthy individuals.

Figure 4. Patients with reported positive DTC screening.

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

Table 3. Table 3. Pathogenic/Likely Pathogenic (P/LP) Mutations in Hereditary Cancer Syndrome Genes in 119,328 Patients Referred for HBOC Genetic Testing Due to Personal or Family History of Breast or Ovarian Cancer.

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).

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