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 variants, 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 reported 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, 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 patients referred for clinical confirmatory testing instigated by positive DTC results from third party analysis of raw data.

Results

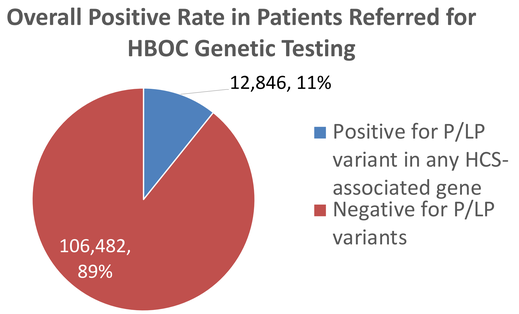

Figure 1. Positive rate of hereditary cancer susceptibility genetic testing in referred patients. P/LP – pathogenic/likely pathogenic, HCS – hereditary cancer susceptibility

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 mutation 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 BRCA1/2 carriers was 88%; rates were 19% and 94% among AJ and non-AJ individuals, respectively (Table 1).

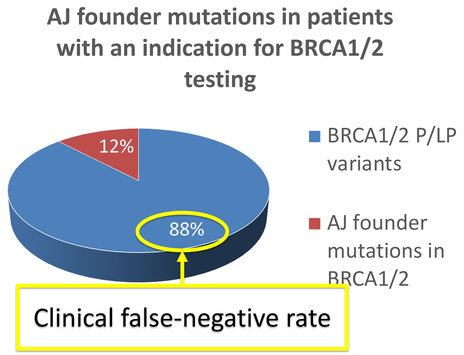

Figure 2. Fraction of AJ founder mutations among patients with a clinical indication for HBOC genetic testing. AJ founder mutation – Ashkenazi Jewish founder mutations including c.68_69delAG (BRCA1), c.5266dupC (BRCA1), c.5946delT (BRCA2).

Patient self-declared ethnicity	Total tested	P/LP mutations in any HCS gene	*BRCA1/2* P/LP mutations among all P/LP mutations in HCS genes (% Total with P/LP mutation)	*BRCA1/2* P/LP that are not AJ *BRCA1/2* founder mutations (% of all *BRCA1/BRCA2* mutations)	*BRCA1/2* P/LP due to 3 AJ founder mutations (% of all *BRCA1/BRCA2* mutations)
Non-AJ	112,681	12,298 (10.9%)	4,346 (35.3%)	4,087 (**94%**)	259† (6%)
AJ	6,647	791 (11.9%)	387 (49%)	73 (**19%**)	315‡ (81%)
Total	119,328	13,089 (11%)	4,733 (36%)	4,160 (88%)	574 (12%)

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).

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 BRCA1/2 mutations in the screening cohort is similar to the indication-based cohort (Figure 3).

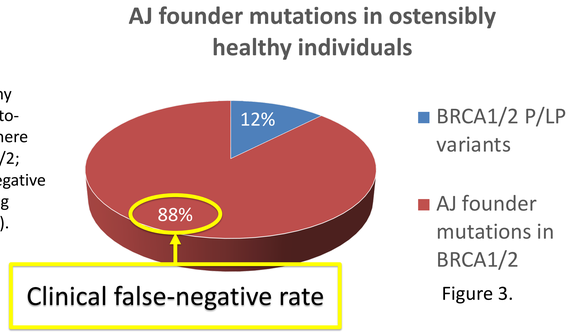

Figure 3.

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 analyses indicated **50%** (52/102) were **analytic false positives** (Fig. 4).

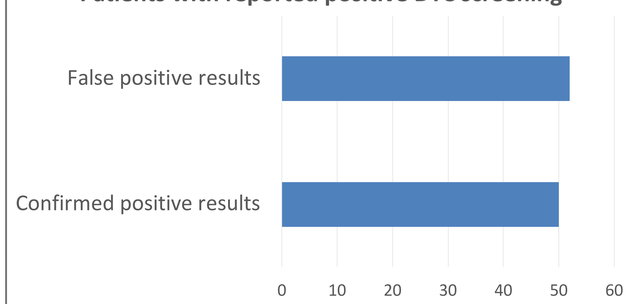

Figure 4. Total number of patients with DTC screening results that underwent confirmation via clinical genetic testing, and the number of patients whose results were found to be analytic false-positives.

Conclusions

- **DTC screening restricted to the Ashkenazi Jewish founder mutations in BRCA1/2 has significant limitations**
- **Clinical false-negative rates were 19% and 94% among AJ and non-AJ individuals, respectively**
- **Despite warnings from the FDA[1], 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[2]**
- **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
1. Food and Drug Administration, https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm599560.htm
2. Walsh T, Mandell JB, Norquist BM, Casadei S, Gulsuner S, et al. Genetic Predisposition to Breast Cancer Due to Mutations Other Than BRCA1 and BRCA2 Founder Alleles Among Ashkenazi Jewish Women. JAMA Oncol. 2017 Dec 1;3(12):1647-1653.