Title:

False Positive Results Reported by Direct-To-Consumer Genetic Tests Highlight the Importance of Clinical Confirmation Testing for Appropriate Patient Care

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False Positive Results Reported by Direct-To-Consumer Genetic Tests Highlight the Importance of Clinical Confirmation Testing for Appropriate Patient Care

There has been an increasing demand from the public for direct-to-consumer (DTC) genetic tests due to greater knowledge about and interest in human genetics and personalized healthcare. While the FDA limits the type of health-related claims DTC tests can market, some DTC companies will provide customers their raw genotyping data if it is requested. While this data often comes with a disclaimer that it is not intended for medical use, it may include alterations occurring in genes which are recommended by the American College of Medical Genetics and Genomics (ACMG) to be reported as incidental or secondary findings in genomic testing. These genes are implicated in highly penetrant genetic disorders for which there are surgical and other interventions available to mutation carriers aimed at preventing or significantly reducing morbidity and mortality. If an alteration in one of these genes is reported to a DTC customer, it is not uncommon for these individuals to request clinical confirmation through their healthcare provider.

Ambry Genetics Corporation is a CAP-accredited and CLIA-approved laboratory that performs clinical diagnostic genetic testing services for a variety of genetic diseases. An internal database search identified 21 patient samples that were received between January 2014 and December 2016 from

patients with previously identified genetic alterations reported by DTC testing. We assessed how often the clinical testing performed at Ambry confirmed the reported DTC results. In addition, clinically relevant personal and family history information reported by the ordering provider was compiled.

Clinical genetic testing at Ambry was performed by Sanger sequencing or next-generation sequencing (NGS), and the results confirmed the reported DTC alteration only 61.9% (13/21) of the time. The remaining 8/21 (38.1%) patients were negative by clinical testing for the DTC reported alterations (false positives). The confirmed alterations occurred in a variety of genes, including BRCA1 and BRCA2 (Hereditary Breast and Ovarian Cancer syndrome), CFTR (Cystic Fibrosis), MEFV (Familial Mediterranean Fever), and CHEK2 (cancer susceptibility). The majority of the confirmed alterations were known pathogenic mutations (10/13). However, in 3/13 of these patients, the confirmed alteration was the same BRCA2 variant which is classified as a benign polymorphism by Ambry (p.N372H).

Notably, amongst the false positive patients, the alterations identified were all previously classified pathogenic mutations occurring in cancer susceptibility genes, including BRCA1, BRCA2, CHEK2, MLH1 (Lynch/HNPCC syndrome), and TP53 (Li-Fraumeni syndrome). None of the eight individuals who had negative confirmation testing were reported to be affected with cancer.

DTC genetic testing has potential clinical utility and its expanding presence is increasing accessibility to genetic testing for the general population, including healthy individuals. DTC testing can identify patients at risk for various genetic disorders that may have otherwise gone undiagnosed. However, our results demonstrate the importance of confirming DTC-reported alterations in a clinical laboratory that is well-versed in complex alteration detection and classification. Clinical confirmation testing, in conjunction with the guidance of a qualified healthcare professional, allows for the appropriate clinical management of accurately identified at-risk individuals.