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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

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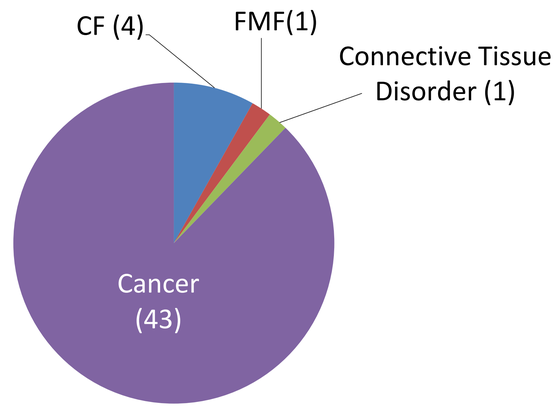
BACKGROUND

- 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.
- DTC genetic testing is increasing accessibility to genetic testing for the general population, including healthy individuals.
- 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 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.

METHODS

- An internal database search identified 49 patient samples that were received between January 2013 and December 2016 from patients with previously identified genetic alterations reported by DTC testing.
- Of the 49 patient samples, there were a total of 26 unique alterations submitted for confirmation.
- We assessed how often the clinical testing performed at Ambry did or did not confirm the reported DTC results.
- Clinical genetic testing at Ambry had been performed by Sanger sequencing or next-generation sequencing (NGS) on all samples.

TYPES OF CASES TESTED



Confirmed Alterations	Frequency	Affected	Unaffected	Unknown
BRCA1 c.68_69delAG	3		3	
BRCA1 c.5266dupC	1		1	
BRCA2 c.5946delT	9	1	6	2
CHEK2 c.1100delC	2		2	
CFTR p.F508DEL	4	2	2	
BRCA1 p.Q356R	1		1	
BRCA2 p.N372H	3	1	2	
CHEK2 p.I157T	1			1
MEFV p.A744S	1	1		
MEFV p.V726A	1	1		
	26 TOTAL			

False Positives	Frequency	Affected	Unaffected
CHEK2 c.1100delC	2		2
TP53 p.R175H	3		3
BRCA1 p.E1250*	1		1
BRCA1 p.A1708E	1		1
BRCA1 p.R1699W	1		1
BRCA2 p.S1955*	1		1
BRCA2 c.9026_9030delATCAT	2		2
BRCA2 p.R2336H	1		1
BRCA2 c.1813dupA	1		1
ATM p.M1040V	1		1
MLH1 p.H329P	1		1
MLH1 c.1101delC	1		1
COL3A1 p.A698T(‡)	1	1 ?	
	17 TOTAL		

False Positive Rate

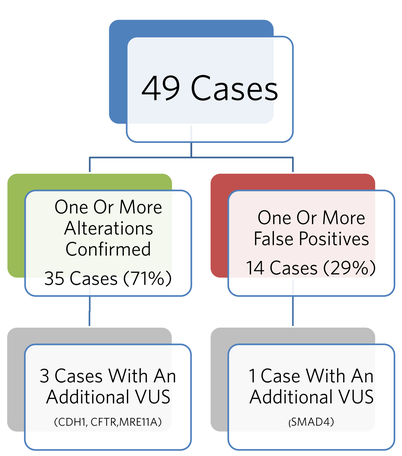
CLASSIFICATION/CLINICAL CONCERNS

- Most of the alterations reported by DTC companies(†) were classified as either a Pathogenic Mutation or VLP by Ambry.
- There were four alterations reported by the DTC companies as putting the individual at an increased risk for a disease, however Ambry's classifications of those alterations were in disagreement.
- There were four deep intronic alterations reported to the consumer that are not routinely covered by panel testing. The alteration locations were provided to Ambry post-testing. (‡)

Gene	Alteration	Classification Provided(†)	Ambry's Classification
ATM	p.M1040V	Increased Risk	Poly
BRCA1	p.Q356R	Increased Risk	Poly
BRCA2	p.N372H	Increased Risk	Poly
COL3A1	p.A698T	Increased Risk	Poly
COL5A1	c.655-8689C>T (‡)	Increased Risk	Deep intronic – poly
COL5A1	c.654+2749A>G (‡)	Increased Risk	Deep intronic – poly
COL5A1	c.1827+399C>T (‡)	Increased Risk	Deep intronic – VUS
COL5A1	c.1827+1142T>C (‡)	Increased Risk	Deep intronic – poly

CASE BREAKDOWN

- 20/49 - we received a copy of the DTC report/raw data
- 29/49 - the alteration was listed on the TRF or in a clinic note



TAKE-HOME POINTS

- 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.
- This study is limited by the small sample size and further studies with larger sample volume would be beneficial.

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