Expecting the Unexpected: Hereditary Cancer and Cardiovascular Findings in an Employer-Sponsored Genetic Testing Program

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Introduction

Genetic testing to assess an individual's risk of developing certain hereditary conditions has become a popular employee benefit in the United States. While there is general support for genetic testing for the CDC Tier 1 genomics applications at the population-level, population-based screening for a broader set of genes remains controversial. Color has partnered with over 100 organizations to offer genetic testing and counseling as an employer-sponsored health benefit. Here, we report the frequency of pathogenic variants in 60 clinically actionable genes that are associated with common hereditary cancer and cardiovascular disorders in 7500 employees, who represent an average-risk cohort. Importantly, as these employees were offered genetic testing independent of testing guidelines, we also evaluated the results with respect to criteria provided by the National Comprehensive Cancer Network (NCCN) as well as personal and family history of cancer and cardiovascular disorders.

Methods

7500 employees received healthcare provider-ordered, next generation sequencing for 60 clinically actionable genes associated with common hereditary cancer (breast, ovarian, uterine/endometrial, colorectal, melanoma, pancreatic, prostate, and stomach) or hereditary cardiovascular disorders (arrhythmias, arteriopathies, cardiomyopathies, and familial hypercholesterolemia [FH]). Laboratory procedures, bioinformatics, and variant classification[1] were performed at the Color laboratory under CLIA and CAP compliance. Results were counted as positive if one or more pathogenic or likely pathogenic (hereafter referred to as pathogenic) variant was detected. Results were delivered with complimentary genetic counseling support.

All individuals gave informed consent to have their de-identified information and sample used in anonymized studies. All personal and family health information was self-reported. Health history was assessed to determine whether individuals met NCCN consideration for genetic testing, as described in the Genetic/Familial High-Risk Assessments for breast and ovarian cancer, colorectal cancer, and gastric cancer.[2]

Conclusions

- Overall, individuals in this cohort were healthier and had little personal or family history of disease.
- The younger age and broad ethnic diversity make this cohort unique, compared to other populations that typically receive multi-gene panel testing.
- Recommendations for genetic testing have been developed based on findings in high-risk cohorts, and as a result, many carriers in unselected populations, such as this cohort, are missed.
- Offering large-scale population-level screening as an employee benefit can help identify hereditary cancer and cardiovascular disease risk in individuals at a young age. Encouraging a more detailed and directed look at personal and family history affords individuals the opportunity to take preventative actions early, and in turn, allows them to better manage and improve their health.

References

1. Richards S, Aziz N, Bale S, et al. Genet Med. 2015.
2. National Comprehensive Cancer Network. (2017). Genetic/Familial High-Risk Assessments for breast and ovarian cancer (version 2.2017), colorectal cancer version (2.2016), and gastric cancer version (1.2017).

Results

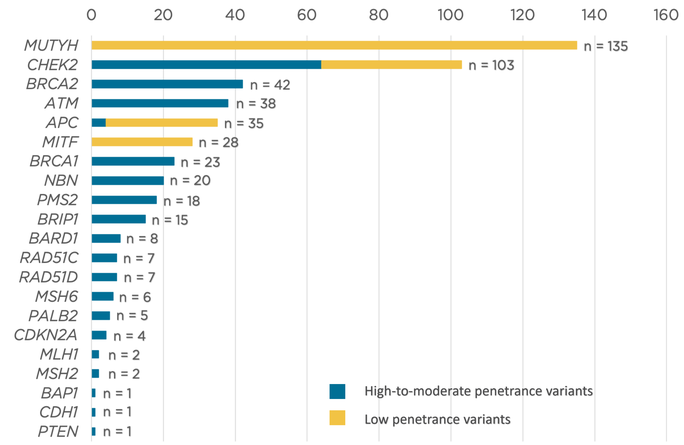
Table 1. Cohort Demographic Details

The majority of individuals who received the Color Test for both both hereditary cancer and cardiovascular disorders (CVD) were women of a Caucasian ethnic background with a median age of 40.7. Pathogenic variants (PV), include low penetrance alleles.

		Individuals (n)	Population	Individuals w/ PV (n)	Pathogenic Frequency
Total		7500	100%	575	7.7%
	Cancer positive			485	6.5%
	CVD positive			97	1.3%
Gender	Female	5053	67.4%	390	7.7%
	Male	2447	32.6%	185	7.6%
Age (Years)	18-30	1869	24.9%	154	8.2%
	31-40	1914	25.5%	145	7.6%
	41-50	1535	20.5%	116	7.6%
	51-60	1515	20.2%	112	7.4%
	61-70	624	8.3%	43	6.9%
	71+	43	0.6%	5	11.6%
Ethnicity	Caucasian	5283	70.4%	408	7.7%
	Multiple Ethnicity	580	7.7%	49	8.5%
	Asian	493	6.6%	36	7.3%
	Hispanic	352	4.7%	14	4.0%
	Ashkenazi Jewish	321	4.3%	48	15.0%
	African	304	4.1%	7	2.3%
	Middle Eastern	50	0.7%	4	8.0%
	Native American	15	0.2%	1	6.7%
	Unknown	102	1.4%	8	7.8%
Personal Cancer History	Any cancer	410	5.5%	44	10.7%
	Breast	97	1.3%	17	17.5%
	Ovarian	16	0.2%	0	0.0%
	Uterine	8	0.1%	2	25.0%
	Colorectal	9	0.1%	2	22.2%
	Melanoma	64	0.9%	6	9.4%
	Prostate	20	0.3%	2	10.0%
	Other cancer	212	2.8%	19	9.0%
	No cancer	7090	94.5%	441	6.2%
Personal Cardiovascular History	Any CVD	631	8.4%	12	1.9%
	No CVD	6869	91.6%	85	1.2%

Figure 1. Genes with pathogenic variants

(A) Pathogenic variants in high-to-moderate penetrance cancer genes were most frequently found in *CHEK2*, *BRCA2*, *ATM*, and *BRCA1*.



(B) Pathogenic variants in high-to-moderate penetrance cardiovascular genes were most frequently found in *MYBPC3*, *LDLR*, *APOB*, *KCNQ1*, *PKP2* and *MYH7*.

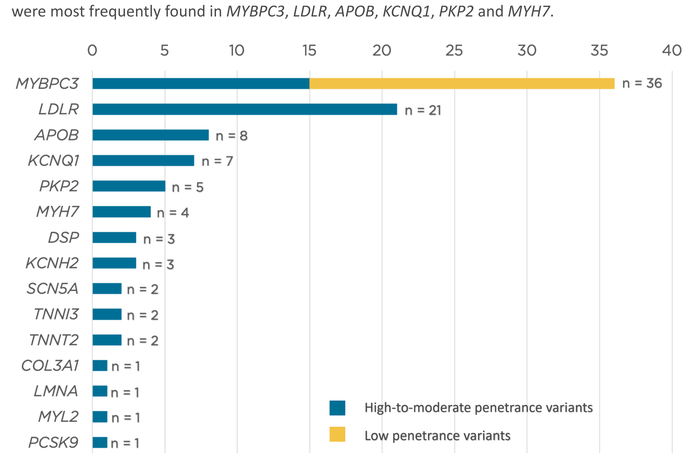
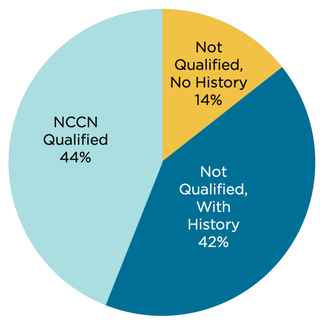


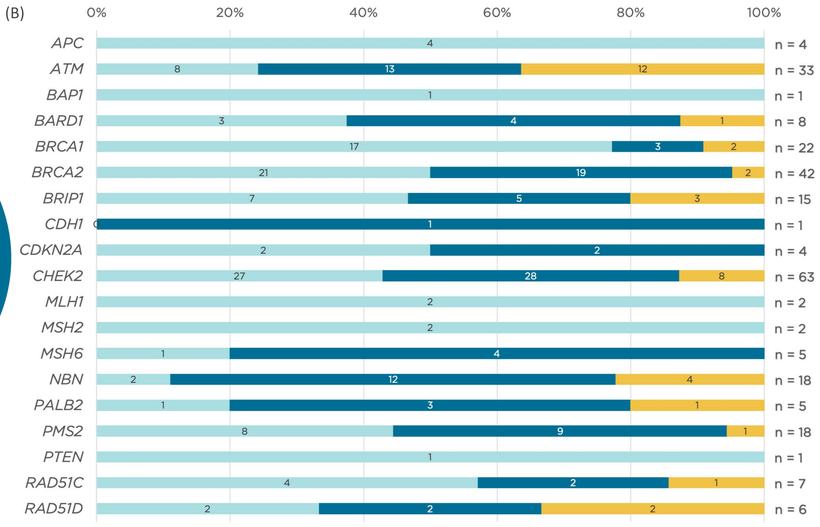
Figure 2. Personal and Family History and Genetic Testing Recommendations by NCCN in Positive individuals

(A) Of the 257 individuals with a high-to-moderate pathogenic variant in a cancer risk gene, 113 (56%) would not have met criteria for testing by NCCN. 37 (14%) of these reported no personal or family history of cancer. (B) Cancer risk gene breakdown by NCCN qualification and personal and family history, with total number of pathogenic variants found in each gene (n).

(A)

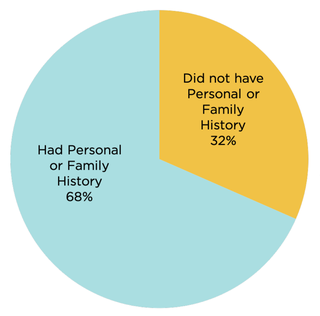


(B)



(C) Of the 76 individuals with a high-to-moderate pathogenic variant in a cardiovascular risk gene, 24 (32%) reported no personal or family history of cardiovascular disease. (D) Cardiovascular risk gene breakdown by personal and family history, with total number of pathogenic variants found in each gene (n).

(C)



(D)

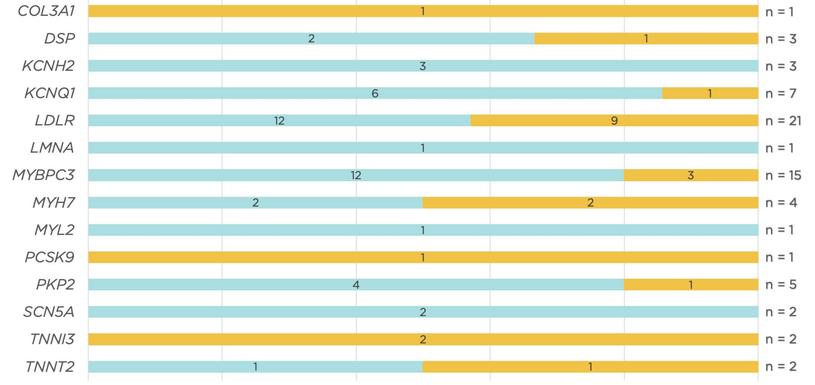
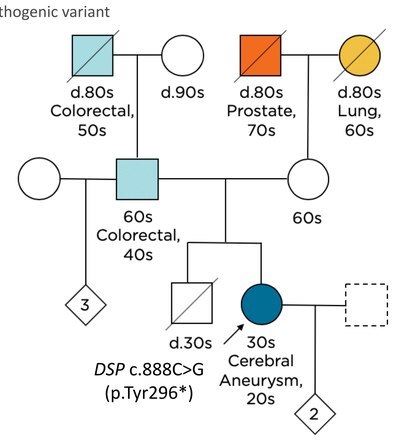
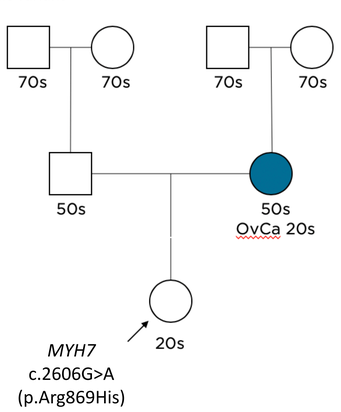


Figure 3. Unexpected Results based on Personal History

(A) An individual with a family history of cancer found to carry a *DSP* pathogenic variant



(B) An individual with a family history of cancer found to carry a *MYH7* pathogenic variant



(C) An individual with no family history of cancer or cardiovascular disease found to carry an *BRCA2* pathogenic variant.