Cascade screening with a large, multi-gene panel test identifies high rate of incidental, clinically actionable findings

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Introduction

The value of genetic testing rests in its ability to prompt appropriate medical actions for the individual being tested and all impacted family members. As such, cascade screening, or testing relatives after identification of a mutation in an individual, is an essential part of high quality clinical genetics care. However, historical uptake of cascade screening is low due to financial, geographic, and legal barriers.[1] Color offers a Family Testing Program (FTP) for relatives to receive simple, electronic communication along with significantly discounted testing. FTP users receive a multi-gene panel, rather than traditional single site analysis for only the known family mutation (KFM).

The FTP was recently updated to include 30 hereditary cardiovascular disease genes in addition to the original 30 hereditary cancer genes. We have previously described outcomes from FTP applicants and the relatives they invited (hereafter referred to collectively as FTP users) who underwent testing for the original 30 hereditary cancer genes.[2] Here, we aim to describe the demographics, uptake rates, and genetic test findings in an expanded cohort which includes the 30 additional hereditary cardiovascular disease genes.

Methods

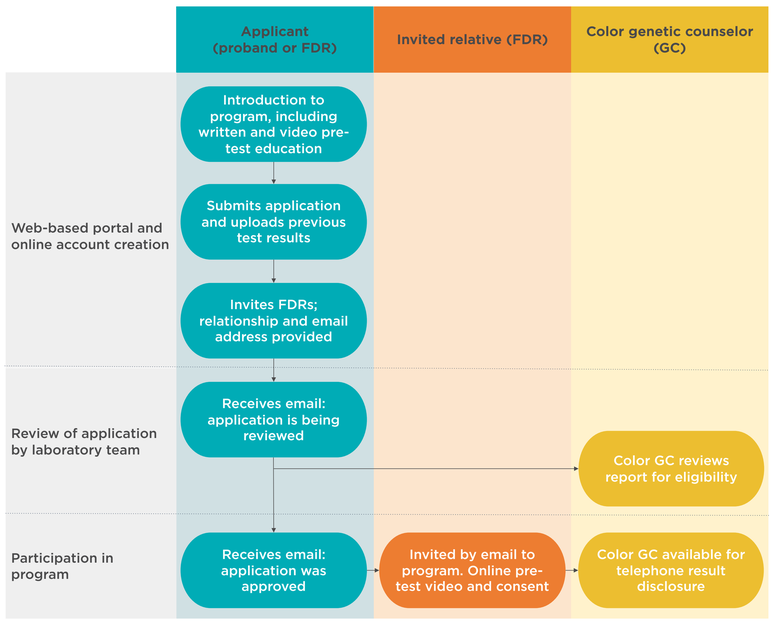
Data from FTP users were analyzed for demographics, uptake rates, and results. Uptake was calculated from the number of invited relatives who followed through by purchasing a Color test. All individuals for which demographic or result information was analyzed consented to have their de-identified information and sample used in anonymized studies. Phenotypic information was self-reported through an online, interactive tool.

FTP User Experience

Individuals who are interested in Color's FTP receive written and video pre-test education via a web-based portal. Any person with a previously identified pathogenic or likely pathogenic variant detected by any Clinical Laboratory Improvements Amendment (CLIA)-certified laboratory in one of 30 hereditary cancer genes or 30 hereditary cardiovascular genes, or their first-degree relatives (FDRs), can apply to the FTP. The individual with a pathogenic or likely pathogenic variant is referred to as the proband, and the individual who submits the application is referred to as the applicant. The proband and applicant may be the same person or FDRs.

The applicant is required to upload a copy of the laboratory report with the pathogenic or likely pathogenic variant, which is reviewed by a Color genetic counselor to ensure eligibility. Color sends an email to the applicant to confirm this process is underway. Once approved by a GC, Color then emails the applicant with an approval notification. A separate email is sent to each of the FDRs of the proband identified by the applicant, inviting them to undergo CLIA-certified multi-gene sequencing via Color Extended, a test which includes the 30 hereditary cancer and 30 hereditary cardiovascular disease genes, at an out-of-pocket cost of US $50. These individuals also receive the same written and video educational pre-test materials. FDR's who were invited to participate are referred to as invited relatives, and collectively with the applicants, as FTP users.

Figure 1. FTP application and testing experience



Results

Table 1. Family testing program participant demographics

Demographics of FTP participants who completed genetic testing at Color (including applicants and invitees, n=3742). FTP participants were mostly female, Caucasian, ages 28-74, and not personally diagnosed with cancer or a cardiovascular condition. Among those participants with a known family mutation (KFM) in cancer, 79.9% reported a family history of cancer.

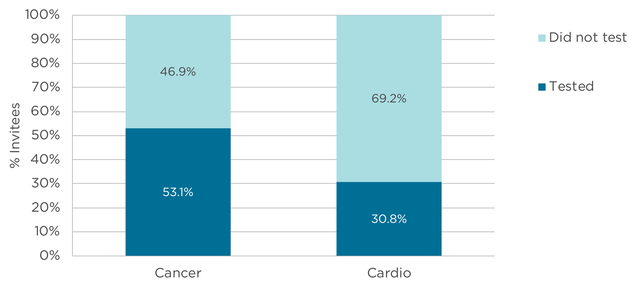
		Color FTP Participants		Color FTP Participants - Cancer		Color FTP Participants - Cardio	
		N	%	N	%	N	%
Total		3742	100.0%	3688	100.0%	54	100
Gender	Male	1451	38.8%	1427	38.7%	24	44.4%
	Female	2291	61.2%	2261	61.3%	30	55.6%
Age	Mean (SD)	48.28	18.11	48.25	18.11	50.08	18.89
	Median (IQR)	47.2	(32.5, 63.4)	47.2	(32.5, 63.4)	50.3	(35.5, 63.6)
Ethnicity	Ashkenazi Jewish	402	10.7%	402	10.9%	0	0.0%
	Asian	94	2.5%	94	2.5%	0	0.0%
	Caucasian	2735	73.1%	2691	73.0%	44	81.5%
	Hispanic	139	3.7%	139	3.8%	0	0.0%
	Multiple Ethnicity	158	4.2%	156	4.2%	2	3.7%
	Other[a]	33	0.9%	31	0.8%	2	3.7%
	Unknown	181	4.8%	175	4.7%	6	11.1%
Test Outcome	Positive	1840	49.2%	1828	49.6%	12	22.2%
	Negative	1902	50.8%	1860	50.4%	42	77.8%
Personal History of Cancer	TRUE	472	12.6%	466	12.6%	6	11.1%
	FALSE	3084	82.4%	3042	82.5%	42	77.8%
	Unknown	186	5.0%	180	4.9%	6	11.1%
Personal History of Cardio[a]	TRUE	172	4.6%	166	4.5%	6	11.1%
	FALSE	1501	40.1%	1477	40.0%	24	44.4%
	Unknown	2069	55.3%	2045	55.5%	30	55.6%
Family History of Cancer	TRUE	2975	79.5%	2946	79.9%	29	53.7%
	FALSE	533	14.2%	515	14.0%	18	33.3%
	Unknown	234	6.3%	227	6.2%	7	13.0%
Family History of Cardio[b]	TRUE	493	13.2%	481	13.0%	12	22.2%
	FALSE	1324	35.4%	1307	35.4%	17	31.5%
	Unknown	1925	51.4%	1900	51.5%	25	46.3%

[a] Other includes African, Middle Eastern and Native American
[b] Individuals were classified as having a personal history of cardiovascular disease if they reported a personal history of any of the following conditions: myocardial infarction, heart failure, arteriopathy, familial hypercholesterolemia, arrhythmia, cardiomyopathy, and/or cardiomegaly
[c] Individuals were classified as having a family history of cardiovascular disease if they reported having a relative who died from a cardiac or unexplained cause

Figure 1. Uptake of family testing from proband applicants

To assess uptake of family testing, analysis was limited to probands who applied to the program (n=2150) and invited their first degree relatives (n=5249). Uptake was higher for invitees with a (KFM) in cancer (53.1%), than cardio (30.8%). Notably, the uptake for cancer is higher than previously reported from the first year of the program's hereditary cancer-only population (47%)[2] and is significantly higher than previous studies of traditional cascade screening approaches (30% on average).[3,4,5]

A)



B)

	Cancer	Cardio
Total number of proband applicants	2097	53
Average number of invitations sent per proband (standard deviation, [range])	2.3 (1.6, [1-11])	2.2 (1.4, [1-7])
Total number of invitations sent	5129	120
Number of invitees who completed genetic testing	2725	37
Number of invitees who did not complete testing	2404	83
Percent uptake	53.1%	30.8%

Figure 2. Results of testing including incidental findings

Test results of invitees (n=3742). The positive rate for the KFM was 46%, as expected. Of note, 5% of users received results that included a different mutation than their KFM, either instead of (3%) or in addition to (2%). One individual whose KFM was in a hereditary cancer gene received a positive result in a hereditary cardiovascular gene.

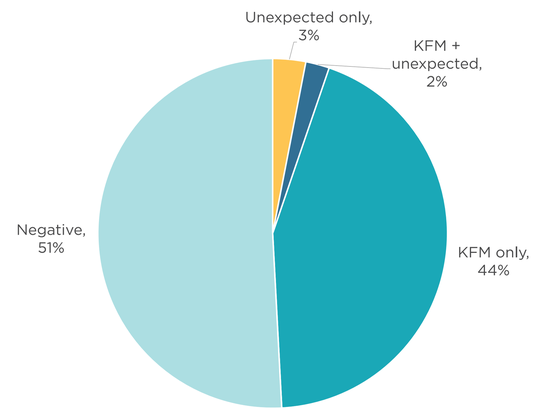
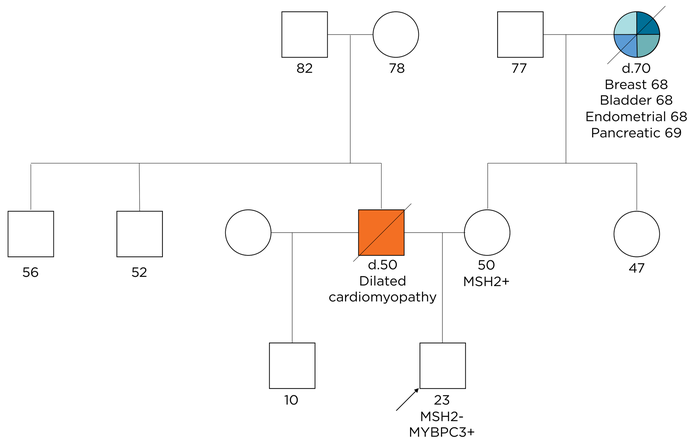


Figure 3. A combination cancer and cardiovascular syndrome family identified through FTP

A 23-year old male enrolled in the Family Testing Program because of his mother's known mutation in the *MSH2* gene, associated with Lynch syndrome. Though he tested negative for that mutation, he tested positive for a previously unidentified mutation in the *MYBPC3* gene, associated with dilated cardiomyopathy. This mutation very likely explains his father's sudden cardiac death caused by dilated cardiomyopathy at age 50.



Conclusions

- Cascade testing uptake was significantly lower for relatives invited to participate because of a known family mutation in a hereditary cardiovascular disease gene compared to hereditary cancer genes.
- Possible explanations for this lower uptake and areas for future research include: less general awareness of hereditary cardiovascular disease genes compared to hereditary cancer genes, and lower perceived efficacy of genetic testing for hereditary cardiovascular disease given widespread heart disease screening in the general population .
- Cascade screening with a large, multi-gene panel in families who were previously receiving more limited testing due to single site testing or small, disease-specific panels may increase detection of clinically actionable findings.
- As previously demonstrated for hereditary cancer, a cascade testing approach for hereditary cardiovascular genes including low cost, seamless online flows, and broad test panels may increase uptake.

References

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