Safety of Multiplex Gene Testing for Inherited Cancer Risk in a Fully Accrued Prospective Trial

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BACKGROUND

- The utilization of multi-gene panel testing for the detection of pathogenic variants is increasing.
- Panel testing enables the investigation of 15 to >100 genes simultaneously.
- Sequencing more genes greatly increases the chance of finding a pathogenic mutation and/or a variant of uncertain significance (VUS).
- Little is known about potential harms of multi-gene panel testing for cancer risk, such as unwarranted surgery or adverse psychological effects.
- Here we investigate the potential risks involved in multi-gene panel testing to determine the safety of their use.

METHODS

COHORT

- Prospective cohort study of multi-gene panel testing, opened August 2014.
- Fully accrued trial (N=2,000)
- Opened in cancer genetics clinics: LA County, USC and Stanford University
- Patients were eligible if they had no prior testing, were age
 ≥18, and had ≥2.5% mutation probability by risk models.

GENETIC TESTING

- The multi-gene panel included BRCA1, BRCA2, ATM, CHEK2, PALB2, NBN, BARD1, PTEN, BRIP1, RAD51C, RAD51D, MLH1, MSH2, EPCAM, MSH6, PMS2, APC, MUTYH, POLD1, POLE, GREM1, BMPR1A, SMAD4, TP53, STK11, CDH1, CDKN2A, and CDK4.
- All genes on the panel were available for the full time period except for *POLD1*, *POLE*, and *GREM1*, which were included starting in July 2016.
- Variants were classified using American College of Medical Genetics and Genomics recommendations, with supporting linkage, biochemical, clinical, functional, and statistical data used for specific missense and intronic alterations.

STATISTICAL ANALYSIS

- Patients completed surveys on testing experiences at entry, then 3, 6, and 12 months thereafter.
- The Multidimensional Impact of Cancer Risk Assessment (MICRA) scale was used to measure distress, uncertainty and positive experiences.

• Of the 2,000 participants with reported results, 12.1% tested positive for a pathogenic mutation, 53.5% tested negative, and 34.5% had VUS only (Table 1).

• The median age was 51, 81% were female, 39% Hispanic, and 73% had a cancer history (Table 1).

Table 1. Patient Characteristics

Category	Total N=2,000	Positive (12.1%)	Negative (53.5%)	VUS (34.5%)			
Gender (n, % by column)							
Female	1,613 (80.7%)	189 (78.1%)	866 (81.0%)	558 (81.0%)			
Male	387 (19.3%)	53 (21.9%)	203 (19.0%)	131 (19.0%)			
Age (years)							
Median (range)	51 (16–92)	53 (22–89)	51 (16–92)	51 (16–92)			
Race (n, % by row)							
Non-Hispanic White	807 (40.4%)	101 (12.5%)	463 (57.4%)	243 (30.1%)			
Non-Hispanic Black	75 (3.8%)	10 (13.3%)	33 (44.0%)	32 (42.7%)			
Hispanic	781 (39.1%)	97 (12.4%)	423 (54.2%)	261 (33.4%)			
Asian	234 (11.7%)	27 (11.5%)	82 (35.0%)	125 (53.4%)			
Language (n, % by column)							
English only	1304 (65.2%)	151 (62.4%)	706 (66.0%)	447 (64.9%)			
Spanish only	519 (26.0%)	67 (27.7%)	290 (27.1%)	162 (23.5%)			
Other	172 (8.6%)	24 (9.9%)	71 (6.6%)	77 (11.2%)			
Education (n, % by column)							
High school or less	601 (30.1%)	79 (32.6%)	325 (30.4%)	197 (28.6%)			
Some college	361 (18.1%)	45 (18.6%)	196 (18.3%)	120 (17.4%)			
College degree or more	797 (39.9%)	83 (34.3%)	423 (39.6%)	291 (42.2%)			
Other or Missing	241 (12.1%)	35 (14.5%)	125 (11.7%)	81 (11.8%)			
Personal Cancer History (n, % by column)							
Affected	1,451 (72.6%)	189 (78.1%)	756 (70.7%)	506 (73.4%)			

• Self reported preventative surgery rates were low (mastectomy 9.2%, hysterectomy 1.6%, oophorectomy 1.8%), with no difference between VUS and mutation negative patients (p=0.207) (Table 2).

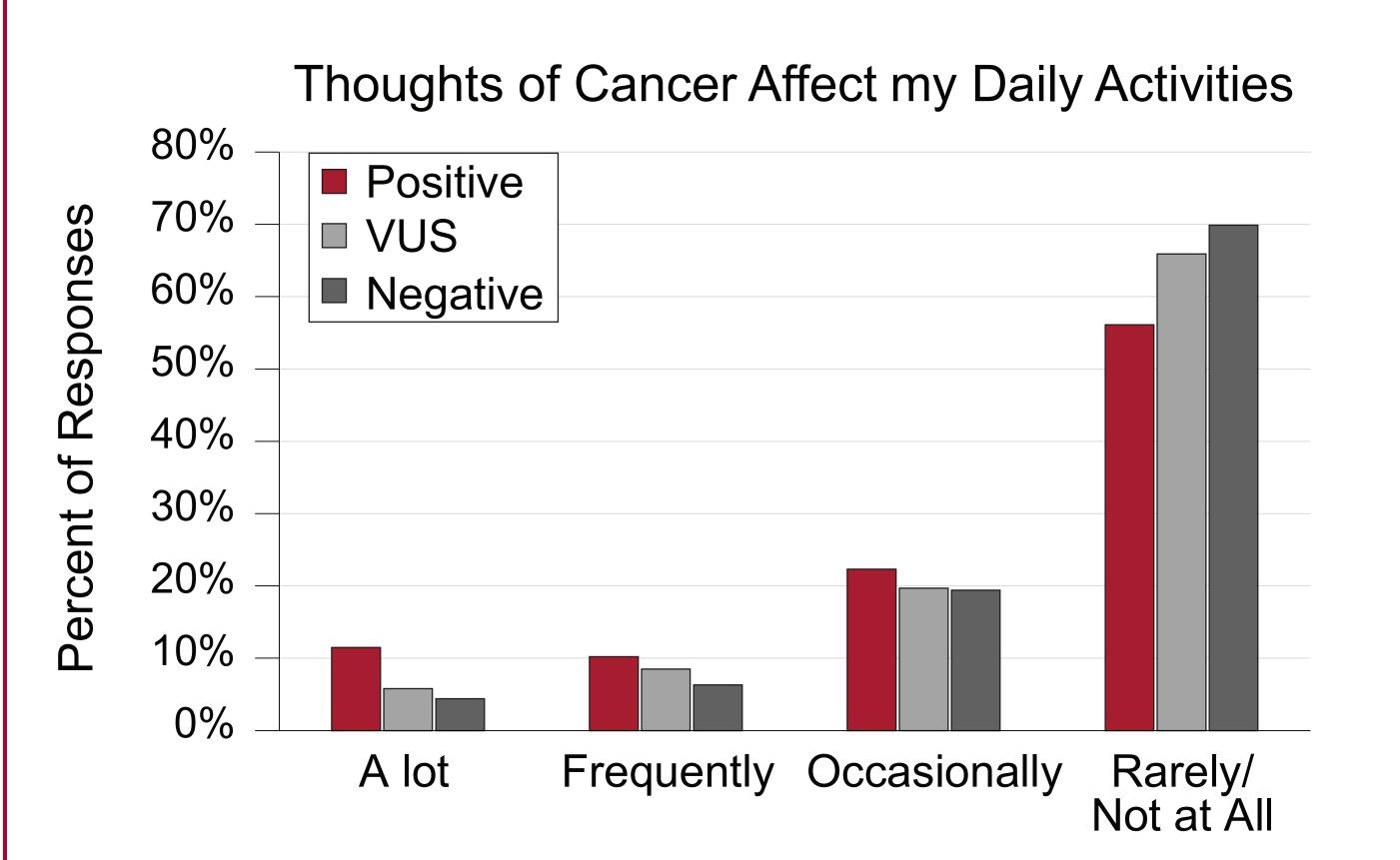
RESULTS

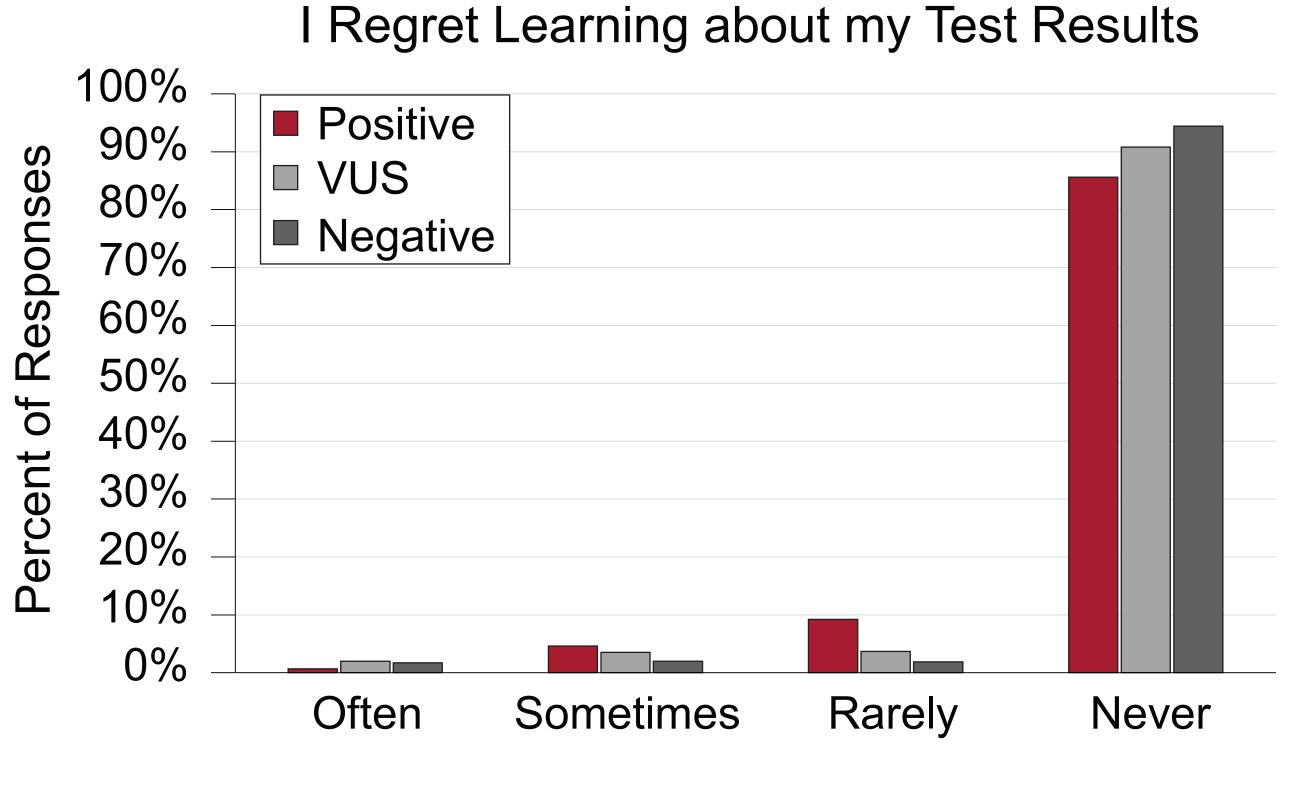
Table 2. Post-Testing Surgical Procedures

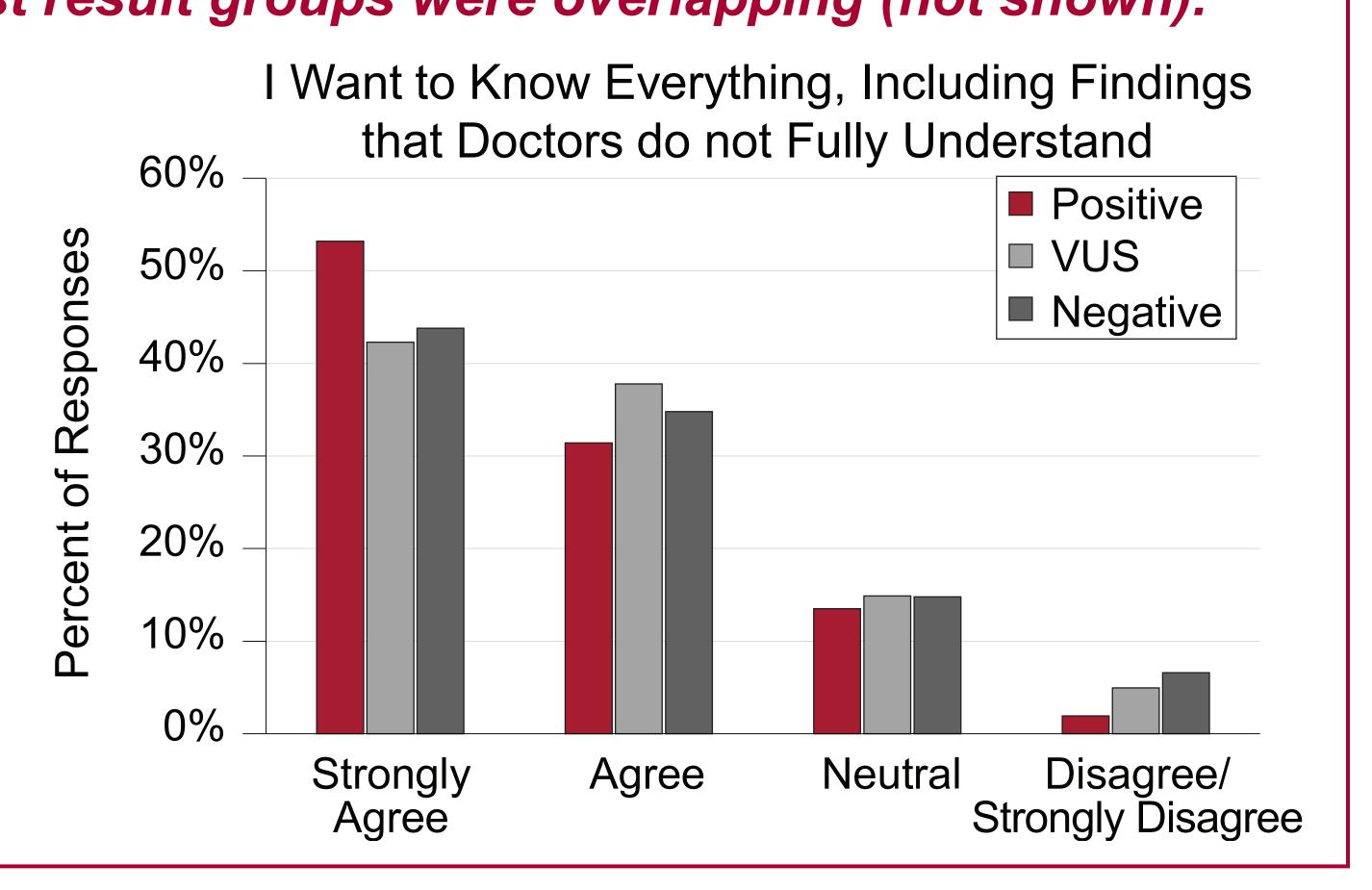
Category	Total N=2000	Positive (12.1%)	Negative (53.5%)	VUS (34.5%)
Mastectomy				
Bilateral	36 (3.3%)	8 (6.3%)	23 (3.8%)	5 (1.3%)
Unilateral	65 (5.9%)	2 (1.6%)	38 (6.4%)	25 (6.7%)
Reason for Mastectomy*				
Cancer Treatment	98 (97.0%)	10 (100%)	59 (96.7%)	29 (96.7%)
Cancer Prevention	23 (22.8%)	4 (40.0%)	15 (24.6%)	4 (13.3%)
Benign Breast Disease	1 (1.0%)	0	1 (1.6%)	0
Hysterectomy				
Yes	12 (1.6%)	6 (8.2%)	5 (1.2%)	1 (0.4%)
Reason for Hysterectomy				
Cancer Treatment	5 (50.0%)	3 (75.0%)	2 (40.0%)	0
Cancer Prevention	1 (10.0%)	1 (25.0%)	0	0
Benign Disease (fibroids)	2 (20.0%)	0	1 (20.0%)	1 (100%)
Oophorectomy				
Bilateral	11 (1.4%)	7 (9.3%)	2 (0.4%)	2 (0.7%)
Unilateral	3 (0.4%)	0	2 (0.4%)	1 (0.4%)
Reason for Oophorectom	y			
Cancer Treatment	6 (50.0%)	3 (50.0%)	3 (75.0%)	0
Cancer Prevention	3 (25.0%)	2 (33.3%)	0	1 (50.0%)
Part of Hysterectomy	2 (16.7%)	0	1 (25.0%)	1 (50.0%)
Part of Hysterectomy *21 women listed different reasons for	2 (16.7%)	0		1 (50.0%)

*21 women listed different reasons for left and right mastectomy and are included twice: 20 listed "Cancer Treatment" and "Cancer Prevention" (4 Positive, 3 VUS, 13 Negative), 1 listed "Cancer Treatment" and "Benign Disease" (Negative).

Figure 1. 3-Month Survey Results Detailing the Perceptions of Genetic Testing. 95% CI between test result groups were overlapping (not shown).



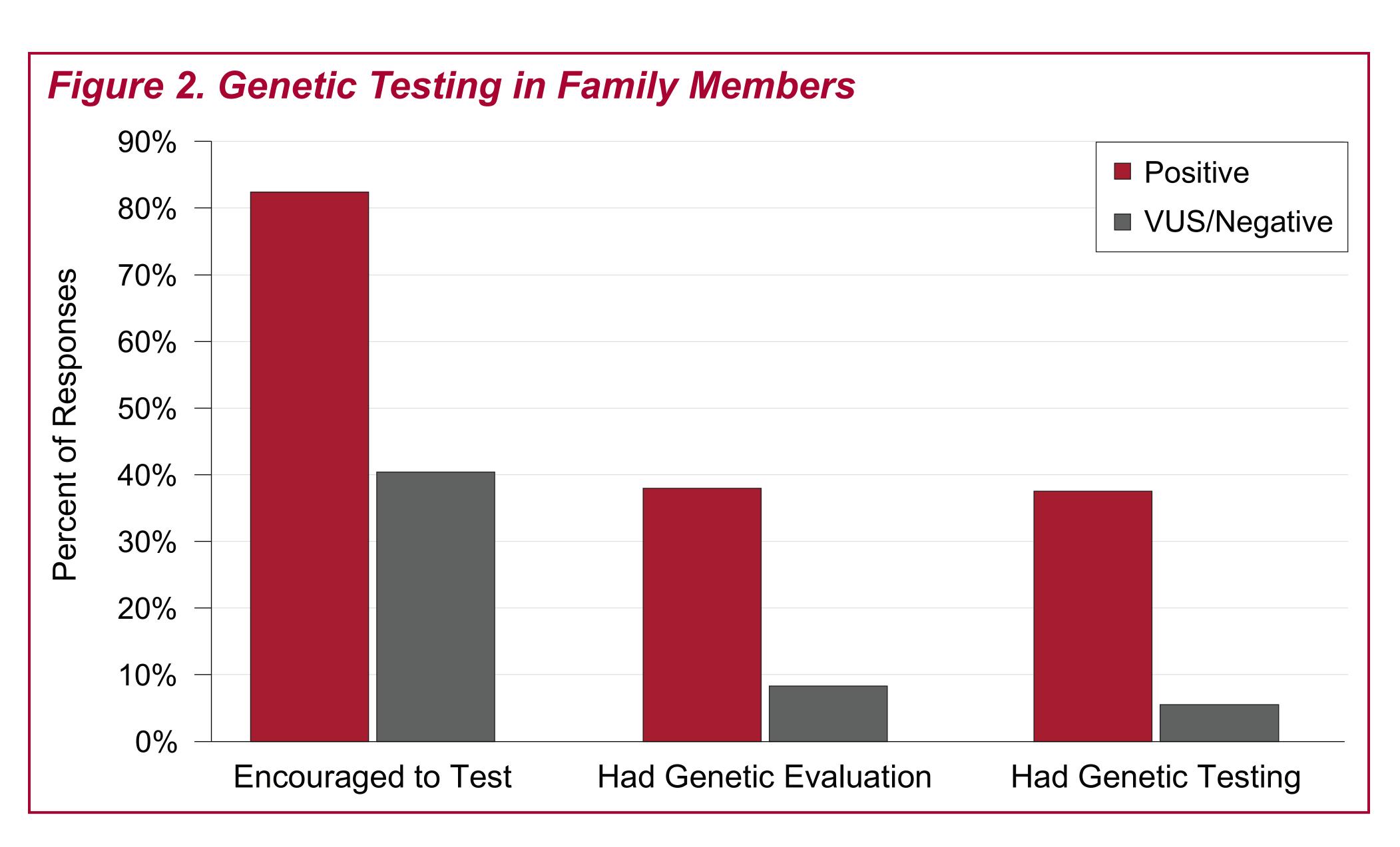




- Most patients never or rarely had thoughts of cancer affecting daily activities, never regretted testing, and wanted to know all results, even those that doctors do not fully understand (Figure 1).
- Mutation positive patients had higher MICRA distress and uncertainty scores than VUS and negative patients, whose distress (p=0.061) and uncertainty (p=0.042) scores were similar (Table 3).
- Relatives of mutation positive patients completed genetic testing more often than VUS or negative patients (Figure 2).

Table 3. MICRA Measurements

MICRA Component	Positive Mean (SD)	Negative Mean (SD)	VUS Mean (SD)
Distress	6.0 (6.07)	1.7 (3.48)	2.2 (4.22)
Uncertainty	10.4 (7.94)	5.9 (6.57)	6.8 (7.08)
Positive Experiences	9.4 (5.13)	11.8 (6.51)	11.7 (6.32)



CONCLUSIONS

- After multiplex testing of 2,000 diverse patients, few reported preventive surgery at 3 months.
- Patients with a VUS had no more distress, regret, or uncertainty than mutation negative patients.
- Mutation positive patients most often advised relatives to test, suggesting that participants understood the implications of test results.
- Follow-up at 6 and 12 months after testing is underway in order to more fully understand the impact of genetic testing in this population.