Abstract 1503: Presented at ASCO 2016

Safety of Multiplex Gene Testing for Inherited Cancer Risk: Interim Analysis of a Clinical Trial

Allison W. Kurian, Gregory Idos, Julie Culver, Charite Ricker, Rachel Koff, Duveen Sturgeon, Katrina Lowstuter, Anne-Renee Hartman, Brian Allen, John Kidd, Courtney Rowe-Teeter, Kerry Kingham, Nicolette Chun, Iva Petrovchich, Meredith Mills, Christine Hong, Kevin McDonnell, Uri Ladabaum, James Ford, and Stephen Gruber

Stanford University Cancer Institute; USC Norris Comprehensive Cancer Center; Myriad Genetics

BACKGROUND

- Multiplex gene panel (MGP) use is increasing
- 15-40 genes instead of only 2 (e.g., *BRCA1/2*)
- Significantly increases the detection of pathogenic mutations
- Complex results: more genes = more variants of uncertain significance (VUS)
- *Does MGP testing cause distress or inappropriate interventions?*

METHODS

- Prospective cohort study of MGP, opened August 2014
  - Goal N=2000, with planned interim analysis after 1000 enrolled
  - Opened in cancer genetics clinics: LA County, USC and Stanford University
- 25-Gene Panel: *APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53*
- Eligibility: No prior testing; age ≥18; ≥2.5% mutation probability by risk models
- Surveys on testing experiences at entry, then 3, 6, and 12 months thereafter
  - Included Multidimensional Impact of Cancer Risk Assessment (MICRA)

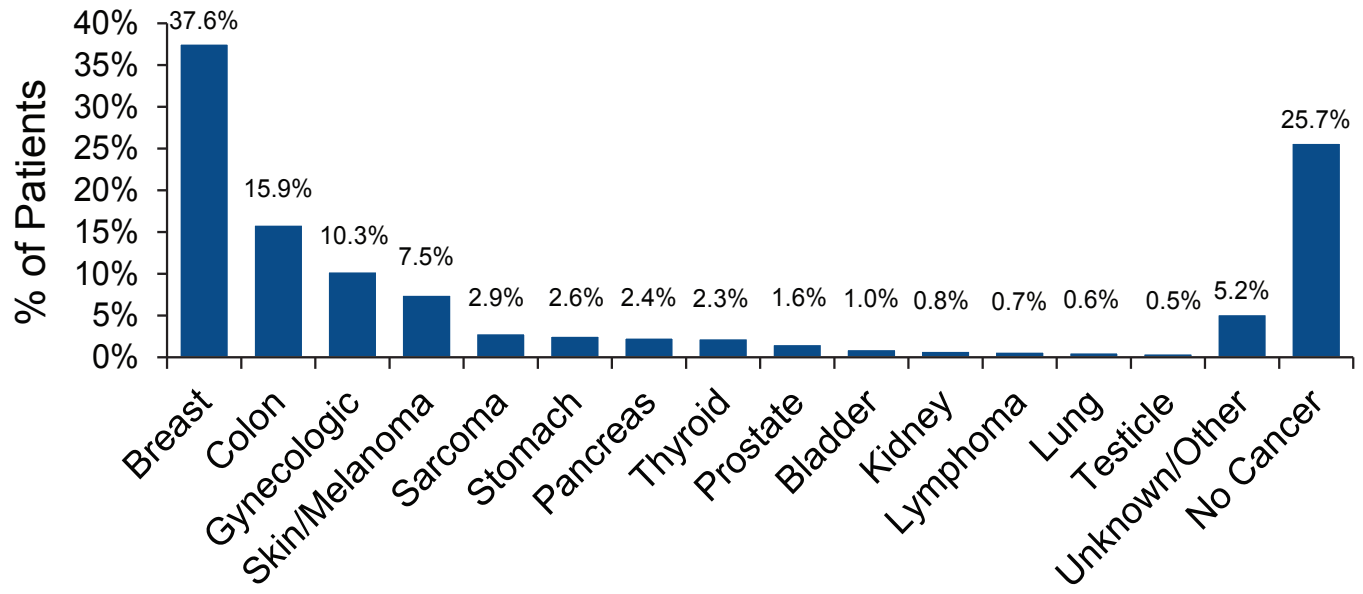
RESULTS

Table 1. Patient Characteristics

Characteristic	Category	Total=1000	Positive (11.6%)	Negative (51.9%)	VUS (36.5%)
Gender	Female (n, %)	**818**	89	420	309
Age	Median, range	**51 (16-92)**	53 (23-89)	51 (19-92)	50 (16-87)
Race	Non-Hispanic White	**383** (38.3%)	39 (10.2%)	235 (61.4%)	109 (28.5%)
	Non-Hispanic Black	**41** (4.1%)	5 (12.2%)	18 (43.9%)	18 (43.9%)
	Hispanic	**404** (40.4%)	52 (12.9%)	205 (50.7%)	147 (36.4%)
	Asian	**129** (12.9%)	20 (15.5%)	34 (26.4%)	75 (58.1%)
Language	English only	**627** (62.7%)	67 (10.7%)	335 (53.4%)	225 (35.9%)
	Spanish only	**292** (29.2%)	34 (11.6%)	153 (52.4%)	105 (36.0%)
	Other	**76** (7.6%)	14 (18.4%)	29 (38.2%)	33 (43.4%)
Education	High school or less	**349** (34.9%)	43 (12.3%)	177 (50.7%)	129 (37.0%)
	Some college	**179** (17.9%)	21 (11.7%)	101 (56.4%)	57 (31.8%)
	College degree or more	**378** (37.8%)	37 (9.8%)	200 (52.9%)	141 (37.3%)
Personal Cancer History	Affected	**743** (74.3%)	96 (12.9%)	375 (50.5%)	272 (36.6%)

- Table 1 shows the clinical characteristics of the cohort
  - 40.4% were Hispanic
  - 29.2% spoke Spanish only
  - 34.9% had a high school education or less
- The most common cancer diagnoses were breast (37.6%) and colon (15.9%) (Figure 1).
  - 25.7% had no history of cancer.

Figure 1. Personal Cancer History



RESULTS

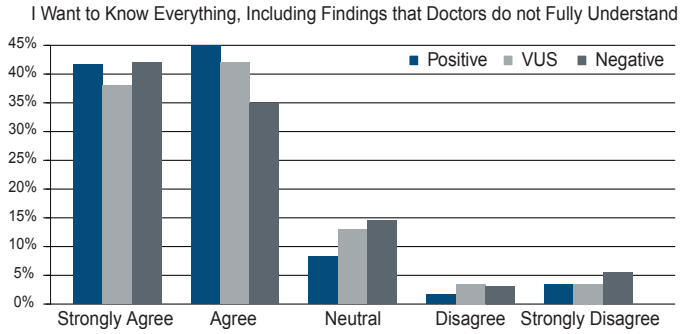
Table 2. Post-Testing Surgical Procedures

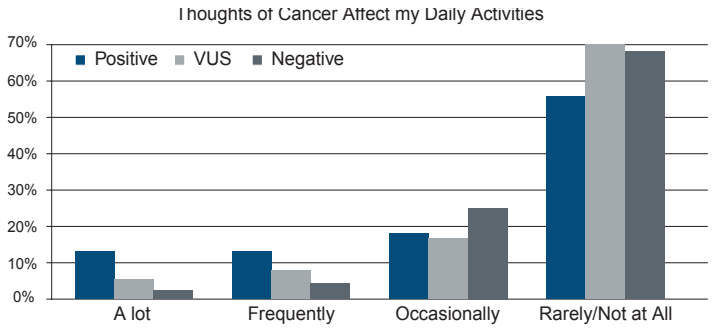
Surgery	Category	Total	Positive (11.6%)	Negative (51.9%)	VUS (36.5%)
Mastectomy	**Bilateral (n, %)**	**17 (3.2%)**	3 (5.2%)	10 (3.6%)	4 (2.0%)
	Unilateral	**31 (5.8%)**	2 (3.4%)	17 (6.1%)	12 (6.1%)
Reason for Mastectomy	**Cancer Treatment**	**47 (97.9%)**	5 (100%)	27 (100%)	15 (93.8%)
	Cancer Prevention	**1 (2.1%)**	0	0	1
	Benign Breast Disease	**1* (2.1%)**	0	1* (3.7%)	0
Hysterectomy	**Yes**	**5 (1.5%)**	2 (7.1%)	2 (1.0%)	1 (0.8%)
Reason for Hysterectomy	**Cancer Treatment**	**3 (60%)**	1 (50%)	2 (100%)	0
	Cancer Prevention	**1 (20%)**	1 (50%)	0	0
	Benign Disease (fibroids)	**1 (20%)**	0	0	1 (100%)
Oophorectomy	**Bilateral**	**3 (0.8%)**	2 (6.5%)	0	1 (0.8%)
	Unilateral	**3 (0.8%)**	0	2 (1.0%)	1 (0.8%)
Reason for Oophorectomy	**Cancer Treatment**	**3 (60%)**	1 (50.0%)	2 (100%)	0
	Cancer Prevention	**1 (20%)**	1 (50.0%)	0	0

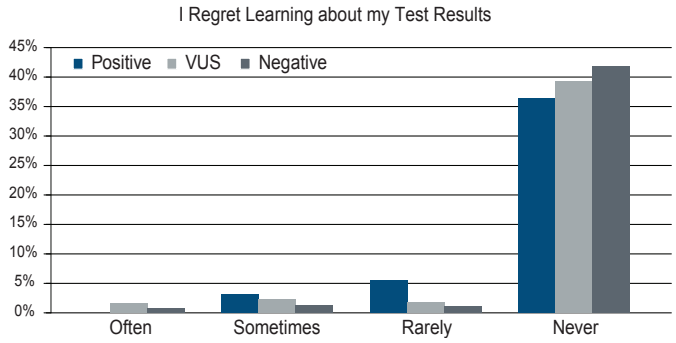
*One patient who had bilateral mastectomy had one breast removed for treatment and the other for benign disease

- All individuals who were found to carry a VUS or no mutation and underwent surgical procedures did so for cancer treatment.

Figure 2: Perceptions of Genetic Testing





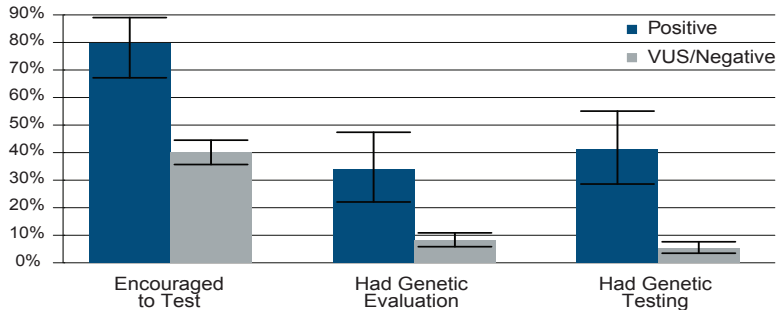


- The majority of individuals wanted to know all test results, rarely thought of cancer that affect their daily activities, and never regretted learning about their test results.
- There were no differences between test result groups (95% confidence interval between test result groups were overlapping - not shown).

- MICRA scores of mutation-positive patients differed significantly from those of negative patients and of VUS patients for all MICRA components ($p<0.001$) (Table 3).
- MICRA scores of VUS patients did not differ significantly from those of negative patients for any MICRA components (p-values 0.06-0.7) (Table 3).

RESULTS

Figure 3. Family Members: Notification and Testing



- Individuals with a mutation were more likely to encourage family members to undergo genetic testing (Figure 3).

Table 3. MICRA Questionnaire

MICRA Component (Mean, SD)	Positive (11.6%)	Negative (51.9%)	VUS (36.5%)
Distress	6.5 (6.68)	2.3 (4.7)	2.5 (4.67)
Uncertainty	12 (8.37)	7.9 (7.89)	6.7 (7.25)
Positive Experiences	9.6 (4.81)	11.9 (6.49)	12.6 (6.35)

CONCLUSIONS

- Multiple-gene panel testing is feasible in a highly diverse population
  - 40% Hispanic, 29% Spanish-speaking only, 35% high school or less
- Little evidence of harm at interim analysis of N=1000
  - Prophylactic surgery rates are low; few had intrusive thoughts or regret
- Notification and testing of relatives appears appropriate
  - Relatives significantly more likely to have testing if proband was positive
- Patients seem to value information despite uncertainty (VUS rate 36.5%)

LIMITATIONS AND QUESTIONS RAISED

- Follow-up time is short (median 3.3 months)
  - Will rates of prophylactic surgery, distress, regret rise?
  - What will happen if/when VUS are re-classified?
- Participating centers have substantial cancer genetics expertise
  - What would happen with less specialized clinical teams?
- Information on relatives' testing was reported by patients
  - Not verified by direct report of relatives, or review of their test results

FUTURE DIRECTIONS

- Complete enrollment of N=2000 (As of June 2016, have enrolled approximately 1500)
- Longer-term follow-up of medical management and chosen interventions
  - Surgery and screening use over time
  - Yield of procedures (cancer detection, subsequent intervention, survival)
- Focused studies of other care settings, patients' relatives are warranted
  - General oncology practice
  - What do clinicians say, vs. what patients/relatives hear?