Abstract 1509: Presented at ASCO 2016

Yield of Multiplex Panel Testing Exceeds Expert Opinion and Validated Prediction Models

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BACKGROUND

- Multiplex gene panel (MGP) testing allows simultaneous analysis of multiple high- and moderate-penetrance genes.
- Increasing use as a clinical genetic testing tool for hereditary cancer risk assessment.
- Increases the detection of pathogenic mutations
- What is the added diagnostic yield of MGP?
- Clinical utility of panels remain to be further delineated.

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 criteria:
  - 1) no previous genetic testing
  - 2) age ≥ 18
  - 3) ≥ 2.5% probability of mutation (by model or clinical index of suspicion)
- Differential diagnoses (DDx) were generated after expert clinical genetics assessment, formulating up to 8 inherited cancer syndromes ranked by estimated likelihood

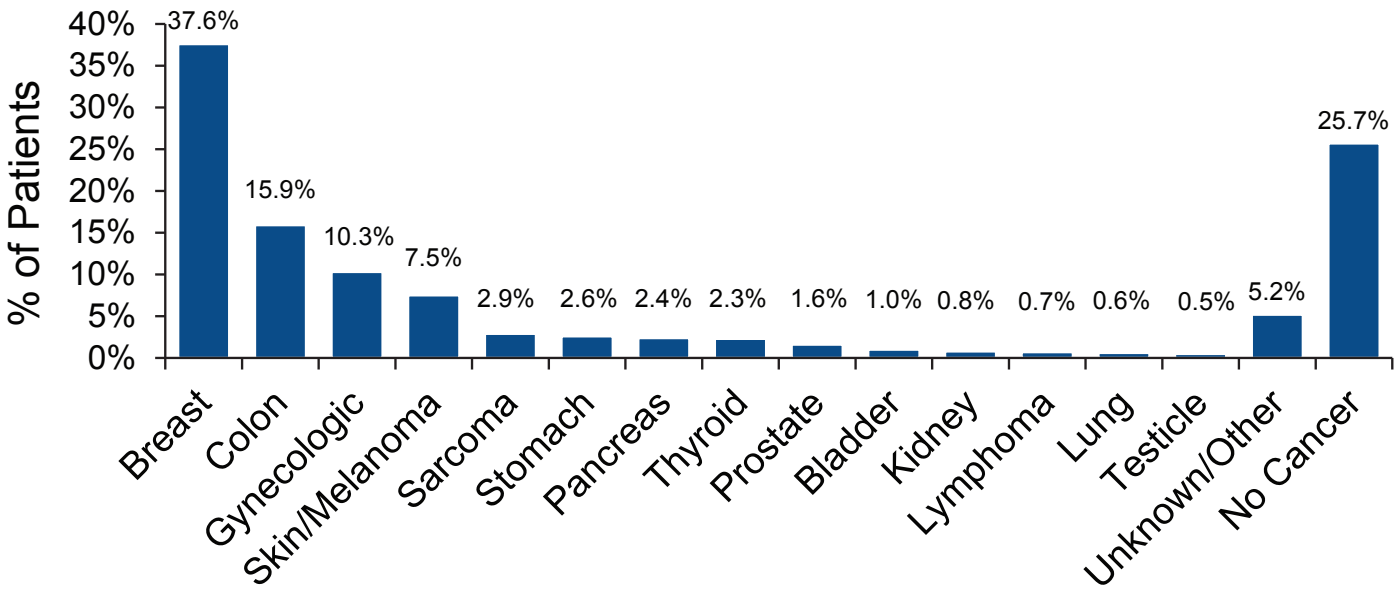
RESULTS

Table 1. Clinical Characteristics

		Total	USC Norris	LAC	Stanford	p-value
Total Patients	N (%)	1000 (100%)	371(37.1%)	396 (39.6%)	233 (23.3%)	n/a
Age at Testing	Mean	51.2	49.9	49.5	56.0	n/a
	Range	23, 89	16, 85	22, 92	17, 89	
Gender	Female	818	279 (75.2%)	337 (85.1%)	202 (86.7%	0.0002
	Male	182	92 (24.8%)	59 (14.9%)	31 (13.3%)	
Ethnicity	Hispanic	404	72 (19.5%)	306 (77.5%)	40 (17.2%)	<0.0001
	Non-Hispanic	596	298 (80.5%)	89 (22.5%)	192 (82.8%)	
Personal History of Cancer (Excluding Skin)	Affected	732 (73.2%)	255 (68.7)	310 (78.3)	178 (76.4)	0.0073
	Not Affected	268 (26.8%)	116 (31.3)	86 (21.7)	55 (23.6)	

- This interim analysis included 1000 patients, 40.4% of whom were Hispanic (Table 1).
- The majority of the cohort (81.8%) was female.

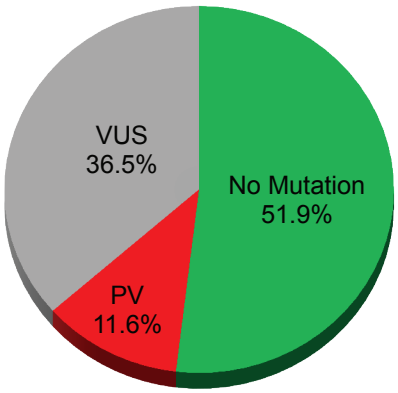
Figure 1. Personal Cancer History



- The majority (73.2%) of patients were affected with cancer at the time of testing.
- Breast (37.6%) and colon (15.9%) cancer were the most common diagnoses (Figure 1).

RESULTS

Figure 2. Pathogenic Variants



- 116 patients tested positive for at least 1 pathogenic variant (11.6%) (Figure 2, Table 2).
- 367(36.5%) patients carried at least 1 variant of uncertain significance (VUS) (Figure 2).
- Figure 3 shows the distribution of genes in which pathogenic variants were identified.
  - The largest proportion of pathogenic variants were identified in *BRCA1* and *BRCA2*.

Table 2. Positive Rate By Ancestry

Ancestry	Total	PV	VUS	No Mutation
Hispanic	404	52 (12.9%)	147 (36.4%)	205 (50.7%)
White, Non-Hispanic	383	39 (10.2%)	109 (28.5%)	235 (61.4%)
Asian	129	20 (15.5%)	75 (58.1%)	34 (26.4%)
African American	41	5 (12.2%)	18 (43.9%)	18 (43.9%)
American Indian/ Alaska Native	3	0	1 (33.3%)	2 (66.7%)
Native Hawaiian/ Pacific Islander	2	0	2 (100%)	0
Unknown/Multiple	38	0	15 (39.5%)	23 (60.5%)
Total	1000	116 (11.6%)	367 (36.7%)	517 (51.7%)

Figure 3. Distribution of PVs

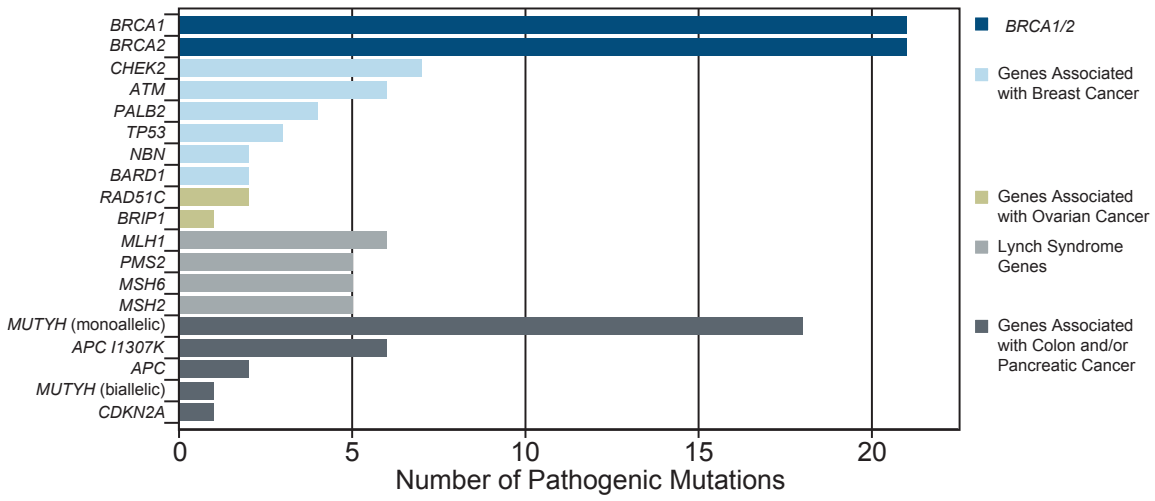
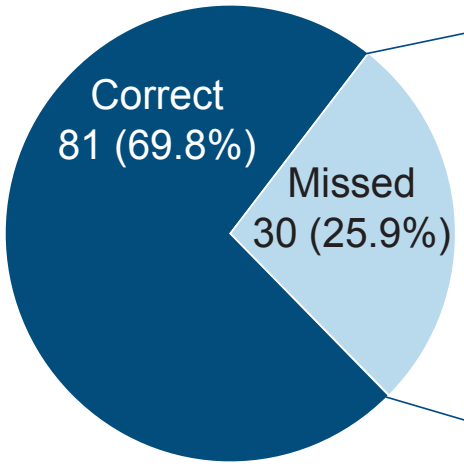


Figure 4: Added Yield with MGP



Gene	N
BRCA1	1
BRCA2	2
PMS2	2
PALB2	2
ATM	3
CHEK2	4

Gene	N
MutYH monoallelic	12
APCi1307k	4

Clinical Implications

- 45y/o female with a family history of mother and sister with endometrial adenoCa at age < 50.
- Differential Dx: *MLH1,MSH2, MSH6, PMS2, EPCAM, PTEN*
- Mutation in *BRCA1*
- 65y/o female with a history of breast ca x2 and sister with breast cancer.
- Differential Dx: *BRCA1/2, PALB2, ATM,CHEK2,NBN, BARD1,RAD51C*
- Mutation in *PMS2*

CONCLUSIONS

- 26% carried pathogenic mutations in unsuspected genes.
  - Suggests a significant contribution of expanded multiplex testing to clinical cancer risk assessment.
  - There is potential for clinically meaningful outcomes with the added value associated with the assessment of multiple genes.
- Identification of unexpected mutations broadens our understanding of cancer risk and genotype-phenotype correlations.
- This study demonstrates the need for increased awareness and utilization of genetic testing for detection of cancer syndromes

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
  - Use of chemopreventive medications
  - Yield of procedures (cancer detection, subsequent intervention, survival)