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

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BACKGROUND

- Multi-gene panel testing allow simultaneous analysis of multiple high- and moderate-penetrance genes.
- There is increasing use of multi-gene panels in clinical genetic testing for hereditary cancer risk assessment.
- The inclusion of multiple cancer-risk genes is expected to increase the detection of pathogenic mutations.
- Here, we assessed the diagnostic yield of multi-gene panel testing in a large, prospective cohort.

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

- Differential diagnoses were generated after expert clinical genetics assessment, formulating up to 8 inherited cancer syndromes ranked by estimated likelihood.
- Differences between the differential diagnoses and genetic testing results were evaluated to determine the added diagnostic yield of multi-gene panel testing.

RESULTS

- Women constituted 80.7% of the total population, and 40.8% were Hispanic (Table 1).
- 242 patients tested positive for at least 1 pathogenic mutation (12.1%) and 689 (34.5%) patients carried at least 1 variant of uncertain significance (VUS) (Table 2).
  - There were no ancestry-based differences in positive mutation rate.
- 72.6% of this cohort was affected with cancer at the time of testing (Table 1), with the most common cancer diagnosis being breast cancer (Figure 1).

Table 1. Patient Characteristics by Site

Category	Total	USC Norris	LAC	Stanford	p-value
Total Patients					
N (%)	2,000	797 (39.9%)	715 (35.8%)	488 (24.4%)	n/a
Age at Testing					
Mean	51.5	50.7	49.5	55.6	< 0.0001
Range	16–92	16–92	21–92	17–90	
Gender					
Female	1,613	591 (74.2%)	609 (85.2%)	413 (84.6%)	< 0.0001
Male	387	206 (25.8%)	106 (14.8%)	75 (15.4%)	
Ethnicity					
Hispanic	816	166 (20.8%)	554 (77.5%)	96 (19.7%)	< 0.0001
Non-Hispanic	1,179	631 (79.2%)	157 (22.0%)	391 (80.1%)	
Personal History of Cancer (Excluding Skin)					
Affected	1,451	549 (68.9%)	554 (77.5%)	348 (71.3%)	0.0007
Not Affected	549	248 (31.1%)	161 (22.5%)	140 (28.7%)	

Table 2. Positive Test Frequency By Ancestry

Ancestry	Total	Positive	VUS	Negative
Non Hispanic, White	807	101 (12.5%)	243 (30.1%)	463 (57.4%)
Hispanic	781	97 (12.4%)	261 (33.4%)	423 (54.2%)
Asian	234	27 (11.5%)	125 (53.4%)	82 (35.0%)
Black or African American	75	10 (13.3%)	32 (42.7%)	33 (44.0%)
American Indian/Alaska Native	5	0	2 (40.0%)	3 (60.0%)
Native Hawaiian or Pacific Islander	5	1 (20.0%)	4 (80.0%)	0
Unknown/Multiple	93	6 (6.5%)	22 (23.7%)	65 (69.9%)
Total	2,000	242 (12.1%)	689 (34.5%)	1,069 (53.5%)

- The most frequently identified mutations were in *BRCA1* (17%, n=41), *BRCA2* (15%, n=36), *APC* (8%, n=19), *CHEK2* (7%, n=17), and *ATM* (7%, n=16) (Figure 2).
- 39 patients (16%) had at least 1 mutation in a mismatch repair (MMR) gene (*MLH1*, n=9; *MSH2*, n=10; *MSH6*, n=8; *PMS2*, n=10, *EPCAM*, n=1, *MLH1* and *PMS2*, n=1) (Figure 2).

Figure 1. Personal Cancer History

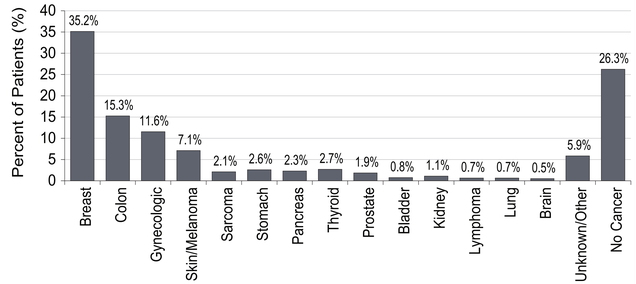
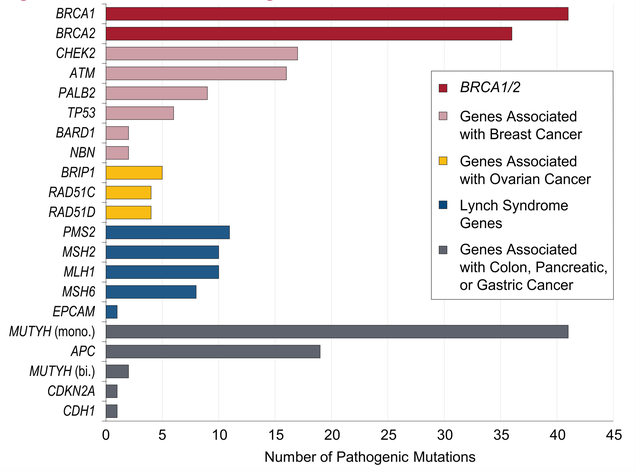
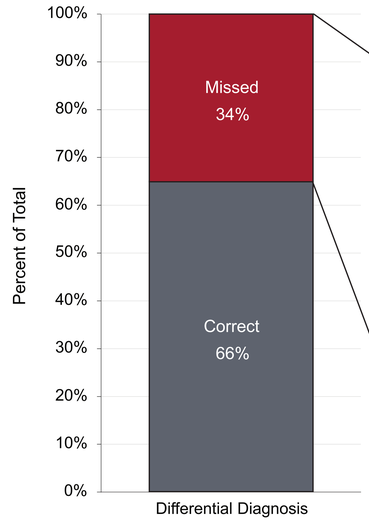


Figure 2. Distribution of Pathogenic Mutations



- 43 individuals (18%) had *MUTYH* mutations, 41 of which were monoallelic.
- Among 19 patients who had pathogenic mutations in *APC*, 16 were *APC* I1307K.
- Only 66% (n=163) of pathogenic mutations were included in the differential diagnosis, and 34% (n=83) of mutations were not clinically suspected.

Figure 3. Added Yield with Multi-Gene Panel Testing



Gene	N
CHEK2	10
PALB2	8
ATM	7
BRIP1	4
BRCA2	3
BRCA1	2
PMS2	2
TP53	1
Monoallelic *MUTYH*	33
APC I1307K	13

CONCLUSIONS

- In a diverse cohort, multi-gene panel testing increased genetic testing yield substantially: 34% of pathogenic mutations were in unsuspected genes, suggesting a significant contribution of expanded multiplex testing to clinical cancer risk assessment.
- The identification of off-target mutations broadens our understanding of cancer risk and genotype-phenotype correlations.
- Follow-up is ongoing to assess the medical and preventive health utilization of participants after multiplex gene panel testing.

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