Interim Analysis of Multiplex Gene Panel Testing For Inherited Susceptibility to Breast Cancer

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Abstract

Background: Emerging evidence demonstrates the effectiveness of targeted gene sequencing panels as a practical method for the diagnosis of inherited susceptibility to breast cancer. Sequencing of multiple high and moderate risk genes simultaneously accelerates the discovery of deleterious mutations (DM) or variants of unknown significance (VUS). However, a consequence of Multiplex Gene panel (MGP) testing is the discovery of unexpected DMs in high or moderate risk genes other than BRCA1 or BRCA2 (BRCA1/2). The overall clinical utility and incremental gain of information conferred by MGP testing in hereditary cancer risk assessment is still unknown.

Methods: We are conducting a multicenter prospective cohort study of patients undergoing cancer-risk assessment using a 25 gene sequencing panel, which includes 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. Patients were recruited from August 2014 to June 2015 at three medical centers. Patients are enrolled if they meet standard criteria for genetic testing or are predicted to have a ≥2.5% probability of inherited susceptibility to cancer calculated by validated risk prediction models. We present a planned interim analysis after enrolling 500 of 2000 total participants.

Results: HCP testing was performed for 332 patients referred for clinical suspicion of hereditary breast and ovarian cancer (HBOC). In this cohort, 96.7% were female (n=321) and the mean age was 50 years (standard deviation, SD=12.2); race/ethnicity was 43.1% Hispanic (n=143), 37% Non-Hispanic White (n=123), 4.2% Black (n=14), 10.5% Asian (n=35), and 1.8% other (n=6) (Table 1). Among this cohort, 37 tested positive for one deleterious mutation (DM) (11.1%: 95% confidence interval (CI), 8.2% to 15%) and 118 patients carried at least one variant of uncertain significance (VUS) (35.5%: 95% CI, 30.6% to 69%) (Figure 1). Excluding BRCA1 or BRCA2, 14 patients (4.3%: 95% CI, 2.6% to 7.2%) have a DM in ATM (n=3), CHEK2 (n=2), MSH6 (n=1), MUTYH (n=3), PALB2 (n=1), PMS2 (n=1), RAD51C (n=2), and TP53 (n=1) (Figure 2). In a patient with an unexpected PMS2 mutation, enhanced cancer surveillance based on Lynch Syndrome guidelines was recommended. Among 160 patients with a history of invasive breast cancer or breast DCIS, 19 patients carried a DM (11.8 %: 95 CI, 7.7% to 17.8%).

Conclusion: In this multicenter prospective cohort study among a diverse group of participants undergoing 25-gene MGP testing, 11.1% of participants tested positive for a DM. Among participants testing negative for BRCA1 and BRCA2, MGP testing identified DMs in 4.3% of participants prompting clinically appropriate risk reduction recommendations and enhanced cancer surveillance. Ongoing recruitment and long-term follow-up are in progress.

Background

- Multigene panel testing is commercially available tool for hereditary cancer risk assessment.
- Next generation sequencing has made it possible to test for mutations within multiple genes in parallel.
- Recent study of multigene panel testing in women with suspected HBOC discovered deleterious mutations in genes other than BRCA1/2.
- It is unclear whether multigene panel testing offers advantages over traditional genetic testing.

Methods

- Multicenter prospective cohort study of patients undergoing cancer-risk assessment using a 25 multi-gene panel (MGP).
- 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 were the following: 1) not previously tested 2) age ≥ 18 3) ≥ 2.5% probability of mutation (by model or clinical index of suspicion) 4) written informed consent.
- Recruited from August 2014 to June 2015 at Los Angeles County Medical Center, USC Norris Comprehensive Cancer Center, and Stanford Cancer Institute.

Results

Table 1. Demographics and Characteristics of Study Participants

Characteristics	Participants with MGP testing for HBOC (n=332) No. Of Participants	%
Age, Years		
Median	50 (12.2)	
Site		
Los Angeles County USC	157	47.3
USC Norris Comprehensive Cancer Center	92	27.7
Stanford Cancer Institute	80	24.1
Sex		
Female	321	96.7
Male	11	3.3
Race/Ethnicity		
NH White,	123	37.0
Hispanic	143	43.1
NH Asian/Pacific Islander	35	10.5
Black	14	4.2
Other race or ethnicity	6	1.8

Abbreviation: MGP, Multi-gene panel testing
HBOC, Hereditary Breast and Ovarian Cancer Syndrome
NH, non-Hispanic
USC, University of Southern California

Results

Figure. 1 Mutation Detection Results

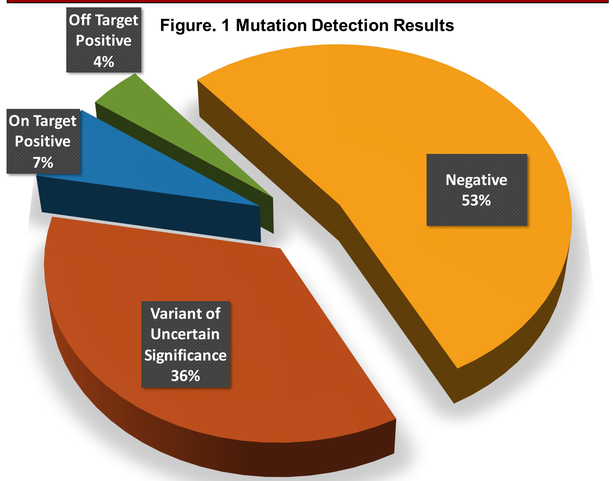
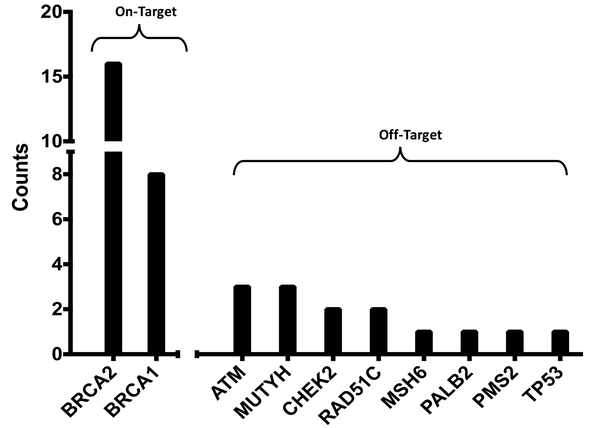


Figure. 2 Deleterious Mutations Identified (N=37)



Results

- Despite a strong family history of breast cancer, a participant was found to carry a mutation in *PMS2* prompting Lynch Syndrome screening recommendations.
- In patients where deleterious mutations were identified, clinical practice guidelines and expert opinion were used to guide risk reduction recommendations.

Conclusions

- 11.1% of participants tested positive for a DM. (Fig. 1)
- Participants testing negative for BRCA1/2, MGP testing identified DMs in 4.3% of participants. (Fig.1& 2)
- Identification of non-BRCA1/2 deleterious mutations prompts appropriate risk reduction recommendations and enhanced cancer surveillance.
- MGP testing may identify subset of patients with deleterious mutations in the context of atypical clinical histories.

Next Steps

- Ongoing study accrual and follow up of participants
- Tracking of genetic test results and clinical outcomes of participants
- Tracking of medical interventions for risk reduction

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