Performance of Mutation Risk Prediction Models in a Racially Diverse Multi-Gene Panel Testing Cohort

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BACKGROUND

- Mutation carrier prediction models are clinically useful tools for identifying candidates for genetic counseling and testing.
- Consensus guidelines recommend germline genetic testing for those with a carrier probability (CP) of approximately 5% or higher.
- However, prediction models may perform less well among racial/ethnic minorities.
- Our hypothesis is that pathogenic mutations are identifiable in a clinically meaningful fraction of racially/ethnically diverse patients with a CP of less than 5%.

METHODS

COHORT

- 2,000 patients were recruited between August 2014 and November 2016 at three medical centers: USC Norris, LAC, and Stanford.
- Patients were enrolled if they met standard clinical criteria for genetic testing or were predicted to have a ≥ 2.5% probability of inherited cancer susceptibility using validated prediction 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.

ANALYSIS

- For patients with a pathogenic mutation in *BRCA1* and/or *BRCA2*, we determined:
  - Whether NCCN testing guidelines for HBOC[1,2] were met.
  - The mutation CP using BRCApro.[3]
- For patients with a pathogenic mutation in one of the mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*), we determined:
  - Whether NCCN testing guidelines for Lynch syndrome[4] were met.
  - The mutation CP using MMRpro[5] and PREMM$_{1,2,6}$.[6]

RESULTS

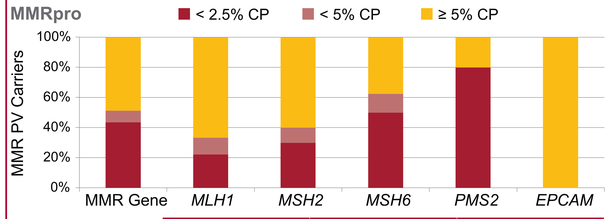
- Of 2,000 patients enrolled in this study, 80.7% were female (n=1,613) and 39.1% (n=781) were Hispanic (Table 1).
- 242 (12.1%) patients tested positive for a pathogenic mutation (Table 1).
- 39 (2.0%) patients had a pathogenic mutation in an MMR gene (Figure 1).
  - Using MMRpro, 17 (43.6%) had any CP < 2.5% and 20 (51.3%) had any CP < 5%.
  - Using PREMM$_{1,2,6}$, 4 (10.3%) had any CP < 2.5% and 13 (33.3%) had any CP < 5%.
- 76 (3.8%) patients had a *BRCA1* and/or *BRCA2* mutation, including 52 (68.4%) who had a BRCApro CP of < 5% (Figure 2).
- 3 (3.9%) patients with a mutation in *BRCA1* or *BRCA2* and 5 (12.8%) patients with a mutation in an MMR gene did not meet current NCCN testing criteria (Table 1).

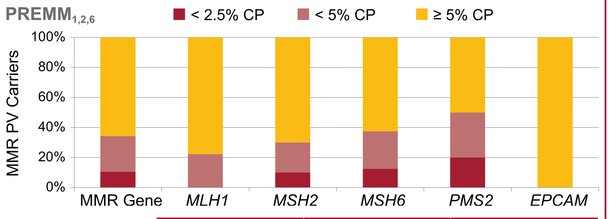
Table 1. Patient Characteristics

Category	Total	Mutation Positive	*BRCA1/2* Positive	MMR Positive
Total	2,000	242 (12.1%)	76 (3.8%)*	39 (2.0%)**
Gender, N (%)				
Female	1,613 (80.7%)	189 (11.7%)	68 (4.2%)	22 (1.4%)
Male	387 (19.4%)	53 (13.7%)	8 (2.1%)	17 (4.4%)
Age, years				
Median (Range)	51 (16-92)	53 (22-89)	51 (27-77)	55 (22-79)
Personal Cancer History, N (%)				
Affected	1,451 (72.6%)	189 (13.0%)	63 (4.3%)	33 (2.3%)
Race, N (%)				
Hispanic	781 (39.1%)	97 (12.4%)	40 (5.1%)	17 (2.2%)
Non-Hispanic white	807 (40.4%)	101 (12.5%)	26 (3.2%)	12 (1.5%)
Asian	234 (11.7%)	27 (11.5%)	4 (1.7%)	6 (2.6%)
Non-Hispanic black	75 (3.8%)	10 (13.3%)	3 (4.0%)	4 (5.3%)
Unknown/Multiple	93 (4.7%)	6 (6.5%)	3 (3.2%)	0
Other	10 (0.5%)	1 (10.0%)	0	0
NCCN Guidelines,† N (%)				
Did not meet 2014 guidelines[1]	—	—	6 (7.9%)	—
Did not meet current guidelines[2,4]	—	—	3 (3.9%)	5 (12.8%)

*Includes one subject who had mutations in both *BRCA1* and *BRCA2*
**Includes one subject who had mutations in both *MLH1* and *PMS2*
†HBOC testing guidelines applied for *BRCA1/2* positive individuals; Lynch syndrome testing guidelines applied for MMR positive individuals

Figure 1. MMRpro and PREMM$_{1,2,6}$ Carrier Probabilities for Individuals with a Mutation in a Lynch Syndrome Gene





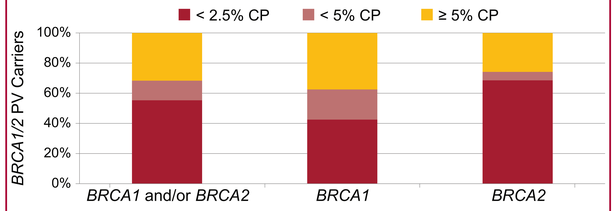
Gene with Mutation	N	MLH1 CP < 2.5% N (%)	MLH1 CP < 5.0% N (%)	MSH2 CP < 2.5% N (%)	MSH2 CP < 5.0% N (%)	MSH6 CP < 2.5% N (%)	MSH6 CP < 5.0% N (%)
Any MMR gene	39	25 (64.1)	30 (76.9)	22 (56.4)	28 (71.8)	29 (74.4)	33 (84.6)
MLH1 only*	9	3 (33.3)	4 (44.4)	3 (33.3)	4 (44.4)	4 (44.4)	6 (66.7)
MSH2 only	10	6 (60.0)	8 (80.0)	4 (40.0)	6 (60.0)	9 (90.0)	9 (90.0)
MSH6 only	8	7 (87.5)	8 (100)	7 (87.5)	8 (100.0)	6 (75.0)	7 (87.5)
PMS2 only*	10	9 (90.0)	10 (100)	8 (80.0)	10 (100)	10 (100)	10 (100)
EPCAM only	1	0	0	0	0	0	0

*1 patient with mutations in both *MLH1* and *PMS2* was excluded.

Gene with Mutation	N	MLH1 CP < 2.5% N (%)	MLH1 CP < 5.0% N (%)	MSH2 CP < 2.5% N (%)	MSH2 CP < 5.0% N (%)	MSH6 CP < 2.5% N (%)	MSH6 CP < 5.0% N (%)
Any MMR gene	39	23 (59.0)	30 (76.9)	20 (51.3)	27 (69.2)	30 (76.9)	36 (92.3)
MLH1 only*	9	2 (22.2)	3 (33.3)	2 (22.2)	3 (33.3)	8 (88.9)	9 (100)
MSH2 only	10	6 (60.0)	8 (80.0)	4 (40.0)	8 (80.0)	6 (60.0)	8 (80.0)
MSH6 only	8	7 (87.5)	8 (100)	5 (62.5)	7 (87.5)	7 (87.5)	7 (87.5)
PMS2 only*	10	8 (80.0)	10 (100)	9 (90.0)	9 (90.0)	7 (70.0)	10 (100)
EPCAM only	1	0	0	0	0	1 (100)	1 (100)

*1 patient with mutations in both *MLH1* and *PMS2* was excluded.

Figure 2. BRCApro Carrier Probabilities for Individuals with a Mutation in BRCA1 and/or BRCA2



Gene with Mutation	N	Any *CP* < 2.5% N (%)	Any *CP* < 5.0% N (%)	*BRCA1 CP* < 2.5% N (%)	*BRCA1 CP* < 5.0% N (%)	*BRCA2 CP* < 2.5% N (%)	*BRCA2 CP* < 5.0% N (%)
BRCA1 or *BRCA2*	76	42 (55.3)	52 (68.4)	53 (69.7)	57 (75.0)	55 (72.4)	61 (80.3)
BRCA1 only*	40	17 (42.5)	25 (62.5)	22 (55.0)	25 (62.5)	29 (72.5)	33 (82.5)
BRCA2 only*	35	24 (68.6)	26 (74.3)	30 (85.7)	31 (88.6)	25 (71.4)	27 (77.1)

*1 patient with mutations in both *BRCA1* and *BRCA2* was excluded.

CONCLUSIONS

- In a diverse cohort of patients undergoing multi-gene panel testing, more than 50% of *BRCA1, BRCA2,* and MMR mutation carriers had a carrier probability of less than 5%, the consensus guideline-recommended threshold for genetic testing.
- In addition, 4% of individuals with a mutation in *BRCA1* or *BRCA2* did not meet NCCN testing criteria for HBOC while 13% of MMR mutation carriers did not meet NCCN guidelines for Lynch syndrome testing.
- Overall, these results support a lower threshold for genetic testing guidelines.

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Presented at ASCO June 5, 2017