Clinical impact of multi-gene panel testing for hereditary breast and ovarian cancer risk assessment

Andrea Desmond[1], Allison W. Kurian[2], Michele Gabree[1], Meredith A. Mills[2], Michael J. Anderson[3], Yuya Kobayashi[3], Nora Horick[1], Shan Yang[3], Kristen M. Shannon[1], Nadine Tung[4,5], James M. Ford[2], Stephen E. Lincoln[3] and Leif W. Ellisen[1,5*]

1. Massachusetts General Hospital Cancer Center, Boston, MA 2. Stanford University School of Medicine, Stanford, CA
3. Invitae Corporation, San Francisco, CA 4. Beth Israel Deaconess Medical Center, Boston, MA 5. Harvard Medical School, Boston, MA

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Background

- **Multi-gene panels are now widely available for assessing hereditary breast and ovarian cancer (HBOC) predisposition.**
- **While consensus management guidelines are longstanding for certain high-penetrance cancer risk genes (e.g. *BRCA1/2*), risk- and gene-based guidelines for management of those with low/ moderate-penetrance genes are only now emerging.**
- **It is not clear how often identifying mutations beyond BRCA1/2 would change clinical management versus personal and family history alone.**

Objectives

- **To determine the prevalence of established hereditary cancer gene deleterious mutations among patients referred for HBOC predisposition testing**
- **To understand the potential impact of identifying these mutations on clinical management**

Clinical Management Analysis

Table 3. **Analysis of Pre- vs. Post-Test Management Change for Patients and Family Members**

Intervention criteria	Relevant genes[1]	Total patients	Intervention	Recommended patients	Family testing[2]
High-risk genes/NCCN management guidelines	*CDH1*, *TP53*, *PTEN*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *APC*, *MUTYH* (biallelic), *BMPR1A*	20	Guidelines-based surveillance/ prevention	20	19 / 19
≥40% breast cancer risk (<40% pre-test risk)[3,4]	*PALB2*[4]	8	Surgical prevention candidate	5[5]	7 / 7
>20% breast cancer risk/NCCN I. 2015 recommendations[6] (<20% pre-test risk)[3,4]	*ATM*[6], *CHEK2*[6], *BRIP1*, *NBN*, *RAD51C*	32	Enhanced breast screening candidate	5	13 / 29
Other cancer risk (pancreas, melanoma)	*CDKN2A*	3	Pancreas screening candidate	3	3 / 3

Post test management change considered for patient; 33/63

Family testing indicated; 42/58

[1] Listed genes are only those found to be mutated in this study.
[2] Family testing recommended if positive result would change management. Only living 1st degree relatives and families with same were considered.
[3]Risk estimates by IBIS (Tyrer Cuzick). Estimates consider both personal and family history.
[4] Risk to age 70. For *PALB2*, risk estimate reflects that all had ≥1 first degree relative with breast cancer.
[5] 3 of 8 patients had undergone prior bilateral mastectomy.
[6]Annual Breast MRI per NCCN guidelines.

Methods

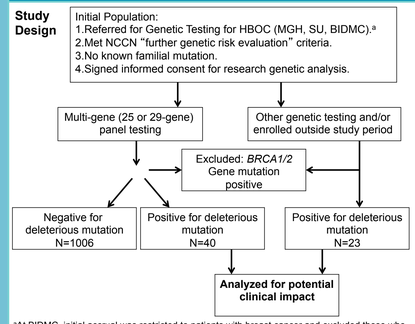
Participants
- 1046 subjects lacking *BRCA1/2* mutations were enrolled prospectively as appropriate candidates for HBOC risk evaluation, per NCCN guidelines. An additional 23 comparable subjects harboring non-*BRCA1/2* mutations were also enrolled.

Procedures
- Research-based clinical laboratory analysis of blood DNA for a 29- or 25-gene panel followed by clinical variant interpretation. Analysis of pre-test versus post-test management recommendations considering gene- and risk-based consensus guidelines and personal/family history.

Measures
- Prevalence of deleterious mutations (DMs).
- Frequency of management change resulting from DMs considering personal and family history.
- Frequency of recommendation for additional family testing among those with DMs.

Results

Study Design



[a]At BIDMC, initial accrual was restricted to patients with breast cancer and excluded those who had positive clinical testing for *BRCA1/2* mutations.

Table 2. **Testing results by gene category and personal history**

Risk Category	Test Result Individuals(%) Any Deleterious	Result by gene subset Mutations(%) High-Risk BR/OV[1]	Mod/Low Risk BR/OV[2]	Lynch[3]	Other Familial Cancer Genes[4]
Total Subjects – 1046	40(3.9)[5]	3(0.3)	26(2.5)	8(0.8)	4(0.4)
BR at any age –832	32(4.0)[6]	2(0.2)	23(2.8)	4(0.5)	4(0.5)
OV at any age –47	5(10.6)	0(0)	2(4.3)	3(6.4)	0(0)
Ashkenazi Jewish –143	1(0.7)	0(0)	0(0)	1(0.7)	0(0)
Cancer Unaffected - 150	4(2.7)	1(0.7)	1(0.7)	2(1.3)	0(0)

Abbreviation: BR/OV: Breast and/or Ovarian Cancer
[1]*TP53*, *PTEN*, *STK11*, *CDH1*
[2]*BARD1*, *CHEK2*, *PALB2*, *ATM*, *BRIP1*, *RAD51C*, *RAD51D*, *NBN*
[3]*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*
[4]*APC*, *BMPR1A*, *SMAD4*, *CDK4*, *CDKN2A*, *PALLD*, *MET*, *MEN1*, *RET*, *PTCH1*, *VHL*, *MUTYH* biallelic
[5]41 mutations among 40 patients; one patient had concurrent *ATM* and *BARD1* mutations.
[6]Numbers in this column do not total 40, as one patient had breast/ovary cancer, and one Ashkenazi patient had ovarian cancer.

Table 4. Summary of deleterious mutations and management changes for patients and family members

Gene	Category	Number of Individuals	Pre- vs. post-test change considered for patient?	Management change considered	Family testing considered?[7]
CDH1	High Risk Breast/Ovary	4	4 of 4	Prophylactic gastrectomy	4 of 4
TP53	High Risk Breast/Ovary	3	3 of 3	Increased cancer surveillance	3 of 3
PTEN	High Risk Breast/Ovary	1	1 of 1	Increased cancer surveillance	1 of 1
ATM [2]	Mod/Low Risk Breast/Ovary	11	1 of 11	Increased breast screening	6 of 11
BRIP1	Mod/Low Risk Breast/Ovary	1	0 of 1	N/A	0 of 1
CHEK2	Mod/Low Risk Breast/Ovary	15	2 of 15	Increased breast screening	4 of 13
NBN	Mod/Low Risk Breast/Ovary	2	0 of 2	N/A	0 of 1
PALB2	Mod/Low Risk Breast/Ovary	8	5 of 8	Increased screening or mastectomy	7 of 7
RAD51C	Mod/Low Risk Breast/Ovary	3	2 of 3	Increased breast screening	3 of 3
MLH1	Lynch Syndrome	1	1 of 1	Increased colorectal/endometrial screening	1 of 1
MSH2	Lynch Syndrome	2	2 of 2	Increased colorectal/endometrial screening	1 of 1
MSH6	Lynch Syndrome	2	2 of 2	Increased colorectal/endometrial screening	2 of 2
PMS2	Lynch Syndrome	4	4 of 4	Increased colorectal screening	4 of 4
APC	Other Familial Cancer	1	1 of 1	Prophylactic colectomy	1 of 1
BMPR1A	Other Familial Cancer	1	1 of 1	Increased gastric cancer screening	1 of 1
CDKN2A	Other Familial Cancer	3	3 of 3	Increased pancreatic surveillance	3 of 3
MUTYH	Other Familial Cancer	1	1 of 1	Increased colorectal screening	1 of 1
Total		**63**	**33 of 63**		**42 of 58**

[7]Family testing recommended if positive result would change management. Only living 1st degree relatives and families with same were considered.
[2]One patient had a concurrent deleterious *BARD1* mutation that was not considered in assessing clinical impact.

Results and Conclusions

- **Non-BRCA1/2 DMs were identified in 3.8% of subjects (40/1046, 95% CI 2.8-5.2%).**
- **The most common DMs involved moderate-risk breast/ovarian cancer genes (ATM, PALB2, and CHEK2) and Lynch syndrome genes, and were consistent with the family cancer history, suggesting that they are clinically significant.**
- **Among all 63 mutation-positive individuals, additional disease-specific screening and/or prevention measures, beyond those based on personal and family history alone, would be considered for the majority (33/63, 52%, 95% CI 40.3 - 64.2%).**
- **Additional familial testing would be considered for most of those with first-degree relatives (42/58, 72%, 95% CI 59.8- 82.2%) based on potential management changes for mutation-positive relatives.**
- **In conclusion, multi-gene testing for HBOC reveals clinically actionable mutations for substantially more patients than does traditional BRCA1/2 testing alone.**

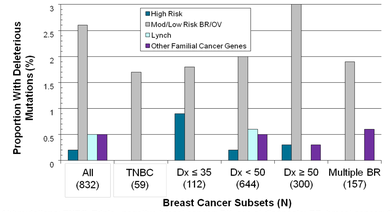
Results

Table 1. **Cohort Demographics**

	MGH/SU Number(%)	BIDMC Number(%)
Total Patients	669	377
Gender		
Male	6(0.9)	3(0.8)
Female	663(99.1)	374(99.2)
Ethnicity		
African	4(0.6)	13(3.4)
Asian	43(6.4)	6(1.6)
Asian Indian	15(2.2)	0(0)
Caucasian	550(82.2)	343(91.0)
Hispanic	27(4.0)	10(2.7)
Multiple	17(2.5)	5(1.3)
Unknown/other	13(1.9)	0(0)
Personal Hx Ca[1]		
Breast Ca	455(68.0)	377(100.0)
Ovarian Ca	40(6.0)	7(1.8)
Colorectal Ca	9(1.3)	1(0.3)
Endometrial Ca	12(1.8)	4(1.1)
Pancreatic Ca	2(0.3)	1(0.3)
No personal Hx Ca	150(22.4)	0(0)

[1]Figures may not add up to 100% due to data not provided or patients with multiple primary tumors reported.

Figure 1. Mutation prevalence among breast cancer patients

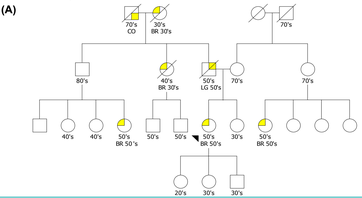


Abbreviations: TNBC. Triple –negative breast cancer; DX, age at diagnosis; BR, breast cancer; OV, ovarian cancer.

Figure 2. Representative case history.

(A) PALB2 c.1240C>T, p.R414X. Finding a PALB2 mutation makes the proband (black triangle), who is already a candidate for enhanced (MRI) breast screening, a possible candidate for prophylactic surgery, and makes the sister, two daughters and potentially other paternal relatives candidates for testing which may alter their recommended screening and prevention options.

(A)



Contact