Clinical Actionability of Panel Tests for Genes in the ~~1.2015~~ 2.2016 NCCN Guidelines for Hereditary Breast and Ovarian Cancer

Andrea Desmond[1], Allison Kurian[2], Shan Yang[3], Kristen Shannon[1], Karen Vikstrom[3], Raluca Kurtz[3], Nadine Tung[4], James Ford[2], Stephen Lincoln[3] and Leif Ellisen[1]

[1]Massachusetts General Hospital, Boston, MA [2]Stanford University Medical Center, Palo Alto, CA [3]Invitae, San Francisco, CA, [4]Beth Israel Deaconess Medical Center, Boston, MA

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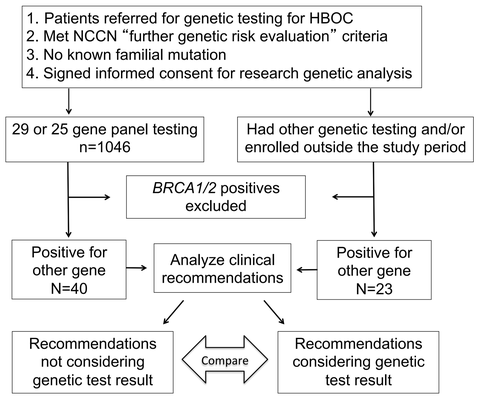
For copies email: steve.lincoln@invitae.com

Background and Objectives

Constitutional (germline) genetic testing is rapidly evolving with the introduction of multi-gene panels, although the clinical impact of such panels is not yet clearly defined. Starting with the 1.2015 version, the NCCN guidelines for genetic/familial high-risk assessment of breast/ovarian cancer now include many additional genes, although limited specific guidance is provided for some of these genes. In recently published work (Desmond *et al.*, *JAMA Oncology* 2015) we began to explore the frequency and types of clinical decisions that may result from multi-gene testing in a representative clinical population. Here we expand upon that work, focusing specifically on those genes mentioned in the NCCN guidelines.

Study Design and Methods

We tested 25-29 genes in over 1000 *BRCA1/2*-negative patients, all of whom were enrolled prospectively at three academic medical centers and all of whom met NCCN guidelines for hereditary breast/ovarian cancer (HBOC) evaluation. We established a uniform algorithm based on the NCCN guidelines to recommend management actions for the non-*BRCA1/2* positive individuals, and we evaluated which of these actions would represent a change in management over and above any recommendations based on personal and family history alone.



Non-*BRCA1/2* genes tested in this study:

NCCN Guideline	Genes	Gene Names
Genetic/Familial High Risk: Breast/Ovarian 1.2015	12	**ATM**, **CDH1**, **CHEK2**, **PALB2**, **PTEN**, STK11, **TP53** Lynch Syndrome: EPCAM, **MLH1**, **MSH2**, **MSH6**, **PMS2**
Genetic/Familial High Risk: Breast/Ovarian 2.2016	15	Same as above, adding: **BRIP1**, **RAD51C**, RAD51D
Genetic/Familial High Risk: Colorectal 2.2015	12	**APC**, **BMPR1A**, **MUTYH**, **PTEN**, SMAD4, STK11, **TP53** Lynch Syndrome: EPCAM, **MLH1**, **MSH2**, **MSH6**, **PMS2**
Pancreatic 1.2016	8	**CDKN2A**, **MLH1**, **MSH2**, **MSH6,** STK11 (**ATM**, **PALB2,** PALLD also mentioned in discussion)
Insufficient Evidence	2	**BARD1**, **NBN**
Not in these NCCN guidelines	6	CDK4, MET, MEN1, RET, PTCH1, VHL

Bold indicates genes with positive findings in the patients in this study.
Note that many genes are in multiple guidelines.

Cohorts:

		MGH/Stanford	BIDMC
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	Breast Ca	455 (68.0%)	377 (100%)
	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 Ca	150 (22.4%)	0 (0%)

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

Figures in this table may not add up to 100% due to data not provided or patients with multiple primary tumors.

The presence of non-*BRCA1/2* mutations in a subset of these patients was previously reported in our prior work:

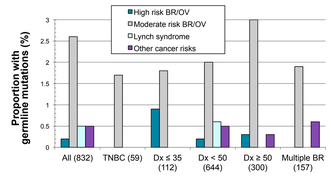
- Tung *et al., Cancer* 2014
- Kurian *et al., JCO* 2014

Mutation Prevalence and Clinical Relevance

63 patients were identified with mutations in non-*BRCA1/2* genes.

- 74% of the cancer-affected patients had a syndromic cancer for the gene they were found to carry. 26% did not.
- However, in 92% of cases, the patient's personal and/or family history was consistent with the syndromic effects of the gene they carry.

Risk category	Any mutation	High risk BR/OV	Moderate risk BR/OV	Lynch syndrome	Other genes
Total subjects – 1046	40 (3.9%)[1]	3 (0.3%)	26 (2.5%)	8 (0.8%)	4 (0.4%)
BR at any age – 832	32 (4.0%)[2]	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%)



Abbreviations: BR Breast Cancer, OV Ovarian Cancer

High risk BR/OV: *TP53, PTEN, STK11, CDH1*
Moderate risk BR/OV: *BARD1, CHEK2, PALB2, ATM, BRIP1, RAD51C, RAD51D, NBN*
Lynch syndrome: *MLH1, MSH2, MSH6, PMS2, EPCAM*
Other cancer risks: *APC, BMPR1A, SMAD4, CDK4, CDKN2A, PALLD, MET, MEN1, RET, PTCH1, VHL, MUTYH*

Footnotes:

[1] 41 mutations among 40 patients; one patient had concurrent *ATM* and *BARD1* mutations. The BARD1 mutation was not considered actionable (see below).

[2] Numbers in this column do not total 40, as one patient had breast/ovary cancer, and one Ashkenazi patient had ovarian cancer.

Clinical Management Impact

We found that the majority of these findings would result in consideration of additional screening and/or prevention measures for the patient. Moreover, testing of first-degree family members would also be warranted given the potential management changes in these individuals if also found to be mutation positive.

Category	Positive genes in this study	Potential change	Patients	Family members[1]
High-risk breast/ovarian 1.2015 guidelines	CDH1, MLH1, MSH2, MSH6, PALB2, PMS2, PTEN, TP53	Guidelines-based surveillance/ prevention	22 of 25	23 of 23
Moderate-risk breast/ovarian 1.2015 and 2.2016 guidelines	ATM, CHEK2	Guidelines-based surveillance	3 of 26	10 of 24
High-risk colorectal or pancreas guidelines (genes not counted above)	APC, BMPR1A, CDKN2A, MUTYH[2]	Guidelines-based surveillance/ prevention	6 of 6	6 of 6
High-risk ovarian, added in 2.2016 guidelines[3]	BRIP1, RAD51C	Guidelines-based prevention	? of 4	? of 4

Management change considered for patient 31/57 (54%)

Family member testing indicated 39/53 (74%)

Gene	Category	Management change considered for patient	Potential management change	Family member testing indicated[1]
CDH1[4]	High risk breast/ovarian	4 of 4	Prophylactic gastrectomy	4 of 4
TP53	High risk breast/ovarian	3 of 3	Increased cancer surveillance	3 of 3
PTEN	High risk breast/ovarian	1 of 1	Increased cancer surveillance	1 of 1
PALB2[5]	Moderate-high risk breast	5 of 8	Increased screening or mastectomy	7 of 7
ATM	Moderate risk breast	1 of 11	Increased breast screening	6 of 11
CHEK2	Moderate risk breast	2 of 15	Increased breast screening	4 of 13
MLH1	Lynch syndrome	1 of 1	Increased colorectal/endometrial screening	1 of 1
MSH2	Lynch syndrome	2 of 2	Increased colorectal/endometrial screening	1 of 1
MSH6	Lynch syndrome	2 of 2	Increased colorectal/endometrial screening	2 of 2
PMS2	Lynch syndrome	4 of 4	Increased colorectal screening	4 of 4
APC	Other colorectal risk	1 of 1	Prophylactic colectomy	1 of 1
BMPR1A	Other colorectal risk	1 of 1	Increased gastric cancer screening	1 of 1
MUTYH[2]	Other colorectal risk	1 of 1	Increased colorectal screening	1 of 1
CDKN2A[6]	Pancreatic/melanoma risk	3 of 3	Increased cancer surveillance	3 of 3
Total		**31 of 57**		**39 of 53**
BRIP1[3]	High risk ovarian	? of 1	*Not yet reevaluated under 2.2016 guidelines*	? of 1
RAD51C[3]	High risk ovarian	? of 3	*Not yet reevaluated under 2.2016 guidelines*	? of 3
NBN[7]	Insufficient evidence	0 of 2	None	0 of 1
BARD1[8]	Insufficient evidence	0 of 1	None	0 of 1
Grand Total		**63**		**58**

Footnotes:

[1] Family member testing recommended if a positive result would change management for that related individual. Only living 1st degree relatives counted here.

[2] Only biallelic MUTYH mutations were considered actionable (autosomal recessive mode of inheritance).

[3] BRIP1, RAD51C and RAD51D were added to the 2.2016 NCCN guidelines as warranting consideration of RRSO. In the previous *JAMA Oncology* analysis these genes had been annotated as moderate-risk for Br/Ov. We have not currently reevaluated these patients in light of the 2.2016 guidelines and they are not included in the totals in this poster. In the previous analysis, 2 of these 4 patients were considered to have potentially actionable findings.

[4] 3 of 4 CDH1 carriers had a family history of gastric cancer, in addition to meeting guidelines for HBOC evaluation. The remaining patient had lobular breast cancer.

[5] PALB2 confers a lifetime risk between approximately 30-60% depending on family history (Antoniou *et al., NEJM* 2014). In the 1.2015 NCCN guidelines a PALB2 finding warranted consideration of increased surveillance, while in the 2.2016 guidelines a PALB2 finding warrants consideration of RRM as well. We had considered RRM recommendations for all PALB2 carriers in the previous *JAMA Oncology* analysis as all positive patients in ourstudy had ≥1 first degree relative with breast cancer.

[6] CDKN2A is not currently mentioned in the NCCN 2.2016 melanoma guideline (it does not currently discuss germline genetics in detail).

[7] NBN is considered to have insufficient evidence in the 2.2016 NCCN guideline. In the *JAMA Oncology* analysis we had considered potential increased surveillance.

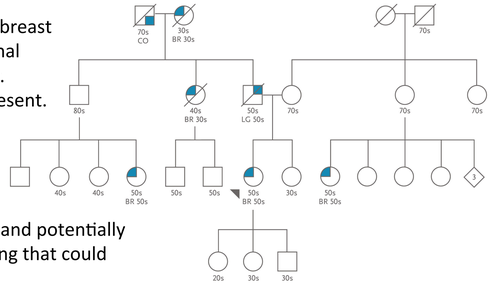
[8] BARD1 is considered to have insufficient evidence in the 2.2016 NCCN guideline. The single BARD1 mutation we saw was in an individual who also had an ATM mutation which informed the management recommendations in this case. BARD1 is not counted in the grand total to have it reflect the number of patients.

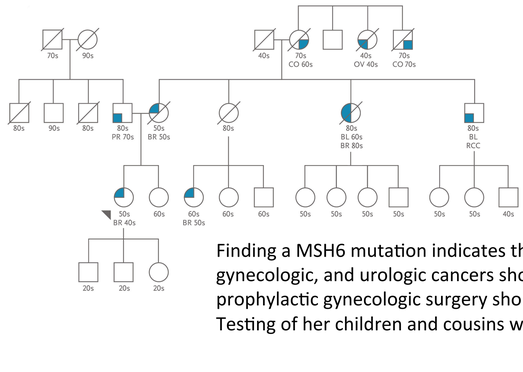
Case Studies

This patient (black triangle) would already have been a candidate for breast MRI screening based on her personal and family history of breast cancer. Colon and lung cancers are also present.

Finding her *PALB2* mutation makes her a possible candidate for prophylactic surgery.

It also makes her sister, daughters and potentially other relatives candidates for testing that could alter their management as well.





This patient (black triangle) has breast cancer with a family history of breast, colon, ovarian, renal, and bladder cancers on her maternal side.

Finding a MSH6 mutation indicates that screening for colorectal, gynecologic, and urologic cancers should be considered, and prophylactic gynecologic surgery should also be considered. Testing of her children and cousins would also be indicated.

Discussion

In this study, potential management recommendations were determined following the NCCN guidelines for genetic testing and were compared to recommendations based on personal and family history alone. Of course, these guidelines have and will continue to evolve, and laboratories should design genetic tests to be easily updated to reflect this.

There were a number of reasons why a patient may not have a management change suggested by a finding in this study:

1. Patient has or had breast cancer: breast screening recommendations were not considered.
2. Patient already had a bilateral mastectomy or oophorectomy as part of their cancer care, in which case RRM/RRSO recommendations were not relevant.
3. Action would already be indicated based on personal and family history alone. We had extensive family histories on all patients, which is not always the case in clinical practice.
4. Lifetime risk was not likely to be >20%.
5. We did not evaluate management changes for patients with negative results (potentially downgrading risk).

We thus likely underestimated actionability, particularly in cases where multi-gene testing could have been done earlier. A further limitation of this study is that we did not consider which of these actions were or would be implemented. This study was performed under a research protocol and return of results (for those patients who had consented to it) is ongoing.

Conclusions

Under the NCCN guidelines, multi-gene testing of appropriately referred patients for breast and ovarian cancer risk evaluation yields clinically relevant findings with potential management impact. These actions are not restricted to breast/ovarian cancer surveillance or prevention, but can include GI, pancreas and other cancers as well. Testing of family members is often indicated based on potential management implications for those individuals. Additional results and discussion are available in our recent publications from this multicenter study:

- Desmond *et al., JAMA Oncology* 2015
- Lincoln *et al., J Molecular Diagnostics* 2015
- Swisher, *JAMA Oncology* 2015 (Commentary)