Multi-gene panel testing for hereditary breast and ovarian cancer risk assessment

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Background

- Multi-gene panels are now widely available for assessing hereditary breast and ovarian cancer predisposition.
- While guidelines are available for those harboring high-penetrance cancer risk genes including BRCA1/2, TP53, PTEN, and CDH1, clinical management recommendations for patients carrying moderate-penetrance genes have not been established.
- It is not clear how often testing patients referred for familial breast/ ovarian cancer risk assessment using multi-gene panels would reveal relevant mutations beyond BRCA1/2, or how often finding such mutations would change clinical management.

Objectives

- To determine the prevalence of established hereditary cancer gene deleterious mutations
- To understand their impact on management of patients referred for hereditary breast and/or ovarian cancer predisposition testing

Subject Demographics

Table 1 . **Clinical Referral Cohort Demographics**

	Number(%)
Total Patients	735
Gender	
Male	84 (11.4)
Female	726 (98.8)
Age at testing (years)	
35 and under	84 (11.4)
<50 (49-36)	260 (35.4)
≥50	391 (53.2)
Ethnicity	
African	6 (0.8)
Asian	48 (6.5)
Asian Indian	17 (2.3)
Caucasian	543 (73.9)
Hispanic	29 (3.9)
Ashkenazi Jewish	59 (8.0)
Multiple	18 (2.4)
Unknown/other	15 (2.0)
Personal Hx Ca*	
Breast Ca	503 (68.4)
Ovarian Ca	42 (5.7)
Colorectal Ca	9 (1.2)
Endometrial Ca	12 (1.6)
Pancreatic Ca	2 (0.3)
No personal Hx Ca	167 (22.7)

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

Methods

Participants

- 735 subjects were collected prospectively as appropriate candidates for breast/ovarian genetic risk evaluation, per standard practice guidelines (Clinical Referral Cohort). An additional 209 subjects were collected retrospectively based on family and personal history (History-Enriched Cohort).

Procedures

- Analysis of blood DNA for a 29-gene panel in a clinical laboratory followed by clinical variant interpretation.

Measures

- Prevalence of deleterious mutations (DMs) and variants of unknown significance (VUS).
- Concordance between testing results from multiple clinical laboratories (see P4-12-07).
- Frequency of management change resulting from DMs considering personal and family history.

Results

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

Risk Category	Any Deleterious	VUS Only[a]	Negative[b]	BRCA1	BRCA2	High-Risk BR/OV[1]	Mod/Low Risk BR/OV[2]	Lynch[3]	Other Familial Cancer Genes[4]
Total Subjects - 735	92 (12.5)	350 (47.6)	293 (39.9)	48 (6.5)	18 (2.4)	1 (0.1)	16 (2.2)	8 (1.1)	1 (0.1)
High-risk BR/OV criteria[c] - 294	39 (13.3)	145 (49.3)	110 (37.4)	21(7.1)	9 (3.1)	0 (0.0)	4 (1.4)	4 (1.4)	1 (0.3)
BR at any age - 503	65 (12.9)	249 (49.5)	186 (37.0)	34 (6.8)	14 (2.8)	0 (0.0)	12 (2.4)	4 (0.8)	1 (0.2)
OV at any age - 42	7 (16.7)	18 (42.9)	17 (40.5)	2 (4.8)	0 (0.0)	0 (0.0)	2 (4.8)	3 (7.1)	0 (0.0)
Ashkenazi Jewish – 59	11 (18.6)	21(35.6)	27 (45.8)	6 (10.2)	4 (6.8)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)
Cancer Unaffected – 167	20 (12.0)	70 (41.9)	77 (46.1)	12 (7.2)	4 (2.4)	1 (0.6)	1 (0.6)	2 (1.2)	0 (0.0)

[a]Not including subjects with deleterious mutations
[b]No VUS or deleterious mutation
[c]Includes subjects with breast (BR) and ovary (OV) cancer; BR or OV cancer with 2 BR/OV-affected relatives; or unaffected with 3 BR/OV-affected relatives. At least one BR-affected relative must be <50.
[1]TP53, PTEN, STK11, CDH1
[2]CHEK2, PALB2, ATM, BRIP1, RAD51C, NBN
[3]MLH1, MSH2, MSH6, PMS2, EPCAM
[4]APC, BMPR1A, SMAD4, CDK4, CDKN2A, PALLD, MET, MEN1, RET, PTCH1, VHL, MUTYH biallelic

Table 3. **Deleterious mutations other than BRCA1/2[1,2]**

Gene	Category	Number	Personal/family history consistent with mutation?[3]	Pre- vs. post-test management change consideration?	Potential Management Change[4]
CDH1	High Risk Breast Ovary	2	1 of 2	2 of 2	Prophylactic gastrectomy
TP53	High Risk Breast Ovary	1	Y	Y	Increased cancer surveillance
ATM	Mod/Low Risk Breast Ovary	7	7 of 7	3 of 7	Increased breast Screening
CHEK2	Mod/Low Risk Breast Ovary	5	4 of 5	3 of 5	Increased breast Screening
PALB2	Mod/Low Risk Breast Ovary	5	5 of 5	5 of 5	Increased breast screening or preventive surgery
RAD51C	Mod/Low Risk Breast Ovary	3	2 of 3	1 of 3	Surveillance or prophylactic ovariectomy
BRIP1	Mod/Low Risk Breast Ovary	1	Y	N	N/A
PMS2	Lynch Syndrome	4	1 of 4	4 of 4	Increased colorectal screening
MSH6	Lynch Syndrome	2	2 of 2	2 of 2	Increased colorectal/endometrial surveillance
MSH2	Lynch Syndrome	1	Y	Y	Increased colorectal/endometrial surveillance
MLH1	Lynch Syndrome	1	Y	Y	Increased colorectal/endometrial surveillance
CDKN2A	Other Familial Cancer	1	Y	Y	Pancreatic cancer surveillance
Total		**33**	**27 of 33**	**24 of 33**	

[1]Among 944 subjects including the 735 Clinical Referral Cohort and 209 History Enriched Cohort
[2]MUTYH monoallelic mutations are not included.
[3]Cancers associated with this gene are present in first, second or third degree relatives.
[4]Including management change for first degree relatives following additional testing. Tyrer-Cuzick model was employed to determine pre-test management of unaffected individuals based on breast cancer risk.

Conclusions

- Potentially relevant DMs were identified in nearly 40% more individuals by multi-gene panel testing (12.5%) than by BRCA1/2 testing alone (9.0%).
- The most common non-BRCA1/2 DMs involved moderate-risk breast/ovarian cancer genes (ATM, PALB2, and CHEK2) and Lynch syndrome genes.
- The majority of the non-BRCA1/2 DMs were consistent with the family cancer history and would result in a clinical management change for patients and/or family members.
- The prevalence of VUS vary by gene and by ethnicity, and nearly 50% of individuals tested for the 29-gene panel had ≥ 1 VUS as the only finding.
- Central collection of data on multi-gene tested patients should be undertaken to accelerate the development of effective management guidelines and to improve outcomes for at-risk individuals.

Results

Figure 1. **Mutation prevalence among breast cancer patients**

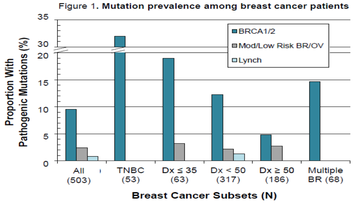
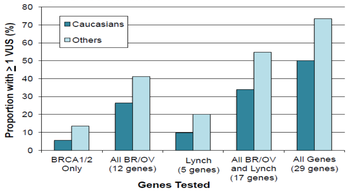


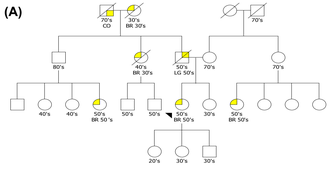
Figure 2. **VUS Prevalence**



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

Figure 3. Representative case histories.

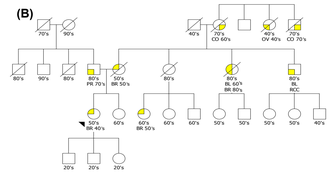
(A)



(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.

(B) MSH6 c.1367G>A, p.W456X. Given an MSH6 mutation in this breast cancer-affected proband with a family history of breast, colon, uterine and bladder cancer, screening for colorectal, gynecologic and urologic cancers would be indicated; prophylactic gynecologic surgery could be considered, and additional family member testing is recommended and could provide indication for enhanced screening and possibly preventive surgery.

(B)



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