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Expanded Panel Testing Superior to BRCA1/2 and Breast Cancer Panel in Patients with Breast Cancer

Findings from the Universal Breast Cancer Genetic Testing Registry

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Background and Significance

NCCN guidelines for genetic testing were established many years ago to identify patients with BRCA 1/2 mutations at a prevalence that seemed economically acceptable and in line with known management implications at the time.

However, the cost of genetic testing has plummeted and management guidelines are developing rapidly. There is a rapid increase in information about the many genes that are linked to breast/ovarian cancer risk (as well as other cancers), resulting in multi-gene panel testing becoming the standard.

We undertook the creation of a Registry: testing all breast cancer patients with a multi-gene panel, whether they met NCCN criteria for testing or not. The primary objective was to determine whether providing *all* breast cancer patients with broad multi-gene panel genetic testing yields additional clinical value by identifying actionable genetic variants including and beyond BRCA 1/2 and if there are any differences in these variants in patients who meet NCCN guidelines and those who do not.

Methods

An IRB-approved multi-center prospective registry was initiated with 20 community and academic breast physician sites experienced in cancer genetic risk testing and management. Sites were selected to support study ethnicity goals commensurate with United States ethnicity demographics. Consecutive patients ages 18-90 years with a current or previous breast cancer who never had genetic testing (either single-gene or multi-gene panel) were offered testing with an 80-gene panel test (Invitae, San Francisco, CA) and consented to be a part of the registry. HIPAA compliant electronic case report forms were used to collect information on patient diagnosis, test results, and physician recommendations made after test results were received. Recruitment goals were 500 patients who met NCCN genetic testing criteria (2017) and 500 who did not.

IRB approval and oversight was provided by WIRB (Puyallup, WA) or via a local IRB.

Results

Over 1000 patients have been enrolled, and data records validated and analyzed for 959. Of these 959 patients, 49.95% met NCCN criteria and 50.05% did not, with a median age of 54 vs. 60, respectively). 67.8% were diagnosed recently; 32.2.% were diagnosed 12 months or longer prior to enrollment. 11.1% had a history of other cancers besides breast.

The variant rate for the entire study cohort is 8.65%. There is a similar rate of P/LP variant rates in the two cohorts: 9.39% of patients who met NCCN criteria; 7.9% of patients who did not meet criteria, with a P value of 0.4241. However, the spectrum of P/LP variants differ between the two groups, with some overlap.

The larger panel yielded a higher variant rate (8.65% vs. 4.9%) than a standard breast cancer guidelines panel (11 genes, which include BRCA1, BRCA2, ATM, CDH1, CHEK2, NBN, PTEN, STK11, TP53, PALB2).

Positive result	BRCA1/2 alone	HBOC 'guidelines' panel (11 genes)	Large Cancer panel (80 genes)
In-criteria	2.51%	6.26%	9.39%
Out-of-criteria	0.63%	3.54%	7.92%

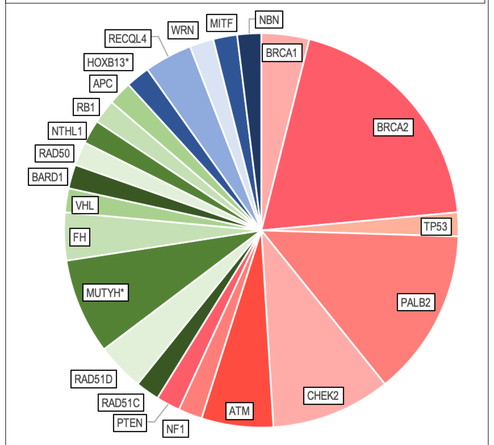
The vast majority (82%) of identified variants have clinical management guidelines, including clinical trials, or yield surveillance recommendations for patients and unaffected family members.

	Patients Meeting NCCN Guidelines	Patients Not Meeting Guidelines
Breast Management Guidelines	30	16
Cancer Guidelines	15	17
Evidence Accruing	6	7

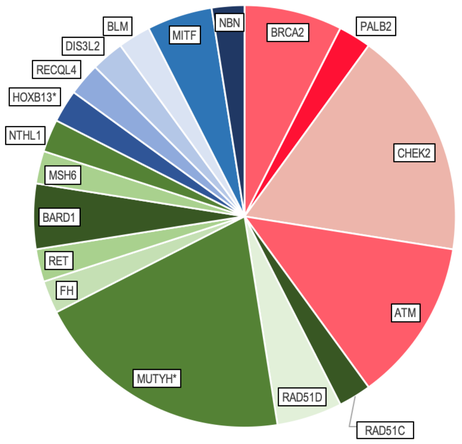
The overall VUS rate was 54.2% for the entire patient population, which is expected when utilizing a larger panel.

Results

Variants in NCCN Patients



Variants in non-NCCN Patients



Actionable Variants

	P/LP Variants	Patients Meeting NCCN Guidelines	Patients Not Meeting Guidelines
With Breast Management Guidelines	BRCA1	2	0
	BRCA2	10	3
	TP53	1	0
	PALB2	7	1
	CHEK2	5	7
	ATM	3	5
	NF1	1	0
	PTEN	1	0
With Cancer Guidelines and Clinical Management Implications	RAD51C	1	1
	RAD51D	2	2
	MUTYH*	4	8
	FH	2	1
	VHL	1	0
	RET	0	1
	BARD1	1	2
	RAD50	1	0
	MSH6	0	1
	NTHL1	1	1
	RB1	1	0
	APC	1	0
Evidence of Actionability Accruing	HOXB13*	1	1
	RECQL4	2	1
	DIS3L2	0	1
	BLM	0	1
	WRN	1	0
	MITF	1	2
	NBN	1	1
Total # variants		51	40
Total # patients		47	39

* Risk Allele

Conclusions

- Universal genetic testing of all breast cancer patients yields a statistically similar incidence of actionable variants as testing patients who meet guidelines.
- Expanded panel testing yields more and a wider variety of pathogenic hereditary variants; there are differences in variants between the cohorts, but most are actionable with present knowledge today.
- Current criteria do not adequately account for the full range of clinical presentations described to date in association with hereditary breast and ovarian cancer; carriers of clinically actionable variants in genes other than *BRCA1/2* are likely to fall outside of current criteria.
- Expanded panel testing with an extensive gene panel can provide information that may present additional treatment and follow-up options, including clinical trials, for all breast cancer patients, not just those who meet criteria for testing.
- A dramatic modification of the scope and intent of the existing genetic testing guidelines is critically overdue to avoid missing patients who may benefit from testing.
- Breast specialists who see their patients over many years are in an excellent position to test and counsel patients on results and make follow up recommendations; this is critical as more information emerges on variants and as guidelines change.

References

National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. Version 2.2019, accessed October 2018.
[b]National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal. Version 1.2018, accessed October 2018.
[c]www.clinicaltrials.gov, accessed October 2018.