Underdiagnosis of Hereditary Breast Cancer: Are Genetic Testing Guidelines a Tool or Obstacle?

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Background and Significance

Approximately 330,000 patients are diagnosed with breast cancer every year in the United States.[1] An estimated 10% of these cancers are likely due to hereditary causes.[2] Studies have estimated that less than 10% of all *BRCA1* and *BRCA2* carriers have been identified.[3] Moreover, 50–80% of individuals at risk have not received genetic testing, in part because they do not meet the family history criteria of current testing guidelines[4,5] and insurance seldom reimburses testing in such cases. An estimated 35,000 breast cancer patients have pathogenic *BRCA1/2* variants, yet only 30% have been identified.[3,4]

NCCN Guidelines were established in an era when testing was very expensive and known management implication s were limited. Today availability of test options have increased, cost of testing has dropped and management guidelines including those relevant to systemic therapy have continued to develop. And yet obstacles including testing guidelines make it challenging to get patients tested and costs covered.

We sought to compare P/LP rates in breast cancer patients who met testing guidelines versus those who did not, Our aim was to understand the capability of 2017-2 NCCN Guidelines to identify breast cancer patients who have variants.

Methods

An IRB-approved multicenter prospective registry was initiated with 20 community and academic breast physicians experienced in genetic testing and management. Sites were selected to help achieve study ethnicity commensurate with United States ethnicity demographics.

Eligibility criteria included all breast cancer patients not previously tested. Consecutive patients were consented and underwent an 80 gene panel test (Invitae –Multi-Cancer Panel). Recruitment goals were 500 patients who meet NCCN genetic testing criteria (2017) and 500 who do not. NCCN Guidelines used were 2017-2.

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

Multi-Panel Gene List (80 Genes)

ALK	APC	ATM	AXZIN2	BAP1
BARD1	BLM	BMPR1A	BRCA1	BRCA2
BRIP1	CASR	CDC73	CDH1	CDK4
CDKN18	CDKN1C	CDKN2A	CEBPA	CHECK2
DICER1	DIS3L2	EGFR	EPCAM	FH
FLCN	GATA2	GPC3	GREM1	HOXB13
HRAS	KIT	MAX	MEN1	MET
MITF	MLH1	MSH2	MSH6	MUTYH
NBN	NF1	NF2	PALB2	PDGFRA
PHOX2	BPMS2	POLD1	POLE	POT1
PRKAR1A	PTCH1	PTEN	RAD50	RAD51C
RAD51D	RB1	RECQL4	RET	RUNX1
SDHA	SDHAF2	SDHB	SDHC	SDHD
SMAD4	SMARCA4	SMARCB1	SMARCE1	STK11
SUFU	TERC	TERT	TMEM127	TP53
TSC1	TSC2	VHL	WRN	WT1

Results

More than 1000 patients were enrolled and data for 959 subjects were analyzed; 49.95% met NCCN criteria and 50.05% did not.

Positive Result	BRCA 1/2 alone	HBOC "guidelines" panel (11 Genes)	Large Cancer Panel (80 genes)
In-criteria	2.51%	6.25%	9.39%
Out-of-criteria	0.63%	3.54%	7.92%

Overall, 8.65% of patients had a pathogenic/likely pathogenic (P/LP) variant. Of patients who met NCCN guidelines with test results, 9.39% had a P/LP variant. Of patients who did not meet guidelines, 7.9% had a P/LP variant. The difference in positive results between these groups is not statistically significant (p = 0.4241, Fisher exact test).

47 patients (4.9%) had P/LP variants if only an 11-gene breast cancer panel was considered, while only 15 patients (1.56%) had P/LP variants if only *BRCA1/BRCA2* were considered

Results

Median age was 54 and 60 respectively.

52% were recently diagnosed (within 12 months) and 48% were diagnosed in the past.

Ethnicity, Cancer History, and Family History were also analyzed.

The spectrum of P/LP variants differ between the two groups, with some overlap.

Importantly, of the patients with P/LP variants who did not meet NCCN guidelines, 56% were eligible for precision treatment and 76% for established management guidelines.

Variants of uncertain significance (VUS) rates were virtually identical between the two groups.

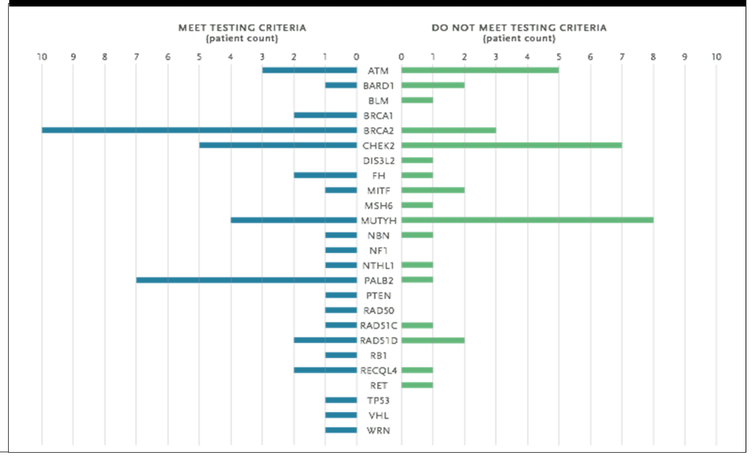
The overall VUS rate was 54.22% for the entire patient population.

Accordingly, almost half of the breast cancer patients tested had either a P/LP variant or a completely negative test with no P, LP, or VUS variants found in 80 genes.

Demographics

	Characteristic	Meet NCCN criteria	Do not meet NCCN criteria
Gender	Female	477 (99.58%)	479 (99.79%)
	Male	2 (0.42%)	1 (0.21%)
Age at initial diagnose	Median	54	60
	Range	24–93	40–89
Ethnicity	African American/Black	33 (6.89%)	30 (6.25%)
	Asian	29 (6.05%)	36 (7.50%)
	Caucasian	389 (81.21%)	383 (79.79%)
	Multiracial	14 (2.92%)	13 (2.71%)
	Native American or Alaskan Native	4 (0.84%)	2 (0.42%)
	Native Hawaiian or other Pacific Islander	2 (0.42%)	9 (1.88%)
	Unknown	8 (1.67%)	7 (1.46%)
Cancer history	With other cancers	54 (11.27%)	52 (10.83%)
	No other cancers	425 (88.73%)	428 (8.75%)
Family history	With positive family history	374 (78.08%)	254 (52.92%)
	No positive family history	102 (21.29%)	221 (46.04%)
	Unknown	3 (0.63%)	5 (1.04%)

P/LP Variants and NCCN Criteria



Conclusions

- Expanded panel testing yields more pathogenic and likely pathogenic variants than BRCA1 or BRCA2 or Breast Cancer Panels with 11 genes.
- Patients who met NCCN genetic testing guidelines have similar likelihood of harboring a variant compared to those who do not.
- Universal genetic testing of all breast cancer patients identifies more patients harboring actionable variants than restricting testing to patients who meet NCCN criteria.
- Current testing guidelines if relaxed would increase access to testing for all breast cancer patients including those in low income or other underserved populations.
- Identifying variants in breast cancer patients opens the door for cascade testing of family member opening up true opportunities for prevention or early intervention.
- Existing guidelines for breast cancer patients should be modified to extend testing to all patients offering them additional management options and to open up testing options for family members.

References

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