Exploring Germline Genetic Testing in Triple-Negative Breast Cancer Patients of Different Ethnicities

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Introduction

- Breast cancer is the most common malignancy in women worldwide and a leading cause of cancer-related mortality.[1]
- Triple-Negative Breast Cancer (TNBC) is a distinct subtype, defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression.[1]
- TNBC accounts for 10–20% of all breast cancers and is often associated with younger age at diagnosis, higher-grade tumors, and aggressive clinical behavior.[2]
- Unlike hormone receptor–positive or HER2-positive subtypes, TNBC lacks targeted therapies and is primarily managed with chemotherapy.[2]
- Recent advances in molecular profiling, immunotherapy, and targeted agents are reshaping the therapeutic landscape.[2]
- Understanding the epidemiology, biology, and treatment challenges of TNBC is crucial to improving outcomes for affected patients.[3]

Methods and Materials

- Data on TNBC patients diagnosed and treated at the King Hussein Cancer Center who underwent germline genetic testing between 2003-2024 were retrospectively collected.
- Genetic Testing was performed on peripheral blood, and sequencing was done at international reference labs.
- Based on the date of testing, some patients underwent limited testing with only BRCA1/2 ± PALB2 (n=150), or an expanded multigene panel (n=434).
- Mutations were classified as benign/likely benign (negative), pathogenic/likely pathogenic (P/LP) (positive), or variant of uncertain significance (VUS).

Patient Characteristics and Demographics

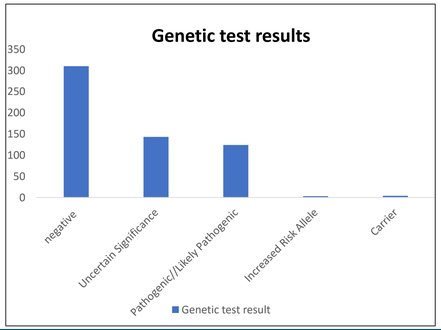
Characteristic	N = 582
Median Age at Diagnosis	45 (37, 54)
Age distribution	
<=39	182 (31.3%)
40-65	364 (62.5%)
>65	36 (6.2%)
Gender	
Female	579 (99.5%)
Male	3 (0.5%)
Other malignancy (non-breast)	
No	548 (94.2%)
yes	34(5.8%)
Family History of malignancy	
Negative	132 (22.7%)
Positive	450 (77.3%)
Breast cancer laterality	
Left	297 (51%)
Right	274 (47.1%)
Bilateral	11 (1.9%)

Characteristic	N = 582
Stage at Diagnosis	
Metastatic	34 (5.8%)
Non-Metastatic	548 (94.2%)
Histopathology	
Invasive breast carcinoma of NOS	553 (95%)
Other	96 (5%)
Tumor grade	
2	104 (18%)
3	470 (81%)
Clinical T stage	
T1-T2	352 (60.5%)
T3-T4	188 (32.2%)
N/A	42 (7.3%)
Clinical N stage	
Negative	265 (45.5%)
Positive	288 (48.5%)

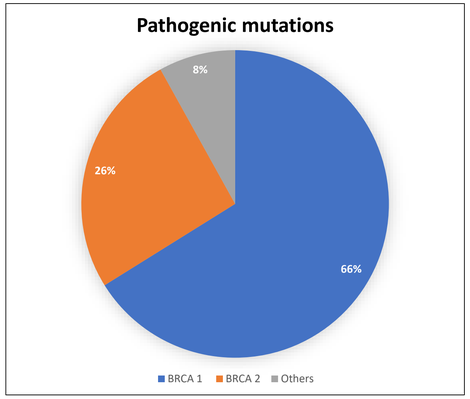
Results

- Genetic testing revealed 310 patients (53.3%) with negative results, 124 (21.3%) with pathogenic or likely pathogenic variants, and 141 (24.2%) with variants of uncertain significance.[3,4]

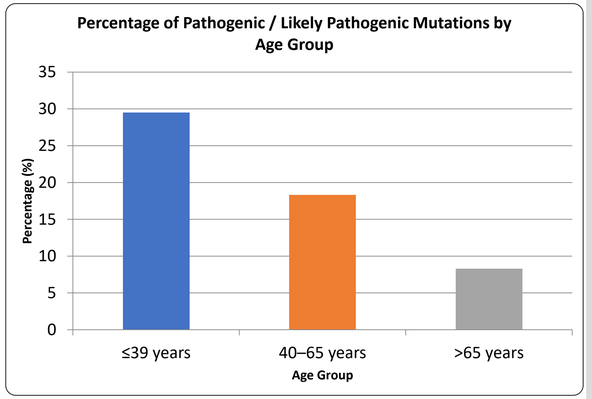
Results of Genetic Testing (n=582)	
Negative	310 (53.3%)
Uncertain Significance	141 (24.2%)
Pathogenic/ Likely Pathogenic	124 (21.3%)
Carrier	4 (0.7%)
Increased Risk Allele	3 (0.5%)



Results



- The frequency of P/LP Mutations was highest in patients younger than 40 years (29.5%) and lowest in those older than 65 years (8.3%), with a statistically significant difference ($p < 0.001$).[3]



- The most common pathogenic variants were found in BRCA1 (82 cases, 66.1%) and BRCA2 (32 cases, 22.8%). Among the 434 patients who underwent multigene panel testing, only 10 (2.3%) carried mutations outside of BRCA1 and BRCA2, with just two involving high-penetrance breast cancer genes (TP53 and PALB2).

Conclusions

- This study highlights the genetic characteristics of TNBC in an Arab population.
- The notably high prevalence of BRCA1 and BRCA2 pathogenic variants reinforces their central role in TNBC tumorigenesis. In resource-limited settings, prioritizing genetic testing for these two genes offers a practical and cost-effective strategy.[3,4]
- Although the prevalence of P/LP variants is significantly lower in patients over 65 years of age, it remains sufficiently substantial to justify continued testing in this group.
- Importantly, over half of mutation carriers opted for risk-reducing surgical Interventions, reflecting the actionable value of genetic findings in clinical decision-making.
- Given that over 96% of patients with pathogenic mutations had a positive family history of malignancy, this highlights the crucial need for implementing cascade genetic testing.

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