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ORIGINAL RESEARCH

The Frequency and Reclassification of Variants Uncertain Significance in Hereditary Breast and Ovarian Cancer Among Levantine Patients

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Introduction: The evolution of genetic sequencing technologies in Hereditary Breast and Ovarian Cancer (HBOC) from BRCA1/2 analysis to multigene panel sequencing was paralleled with a significant increase in the number of detected variants of uncertain significance (VUS). This trend was found to particularly affect minority populations, such as the underrepresented Middle Eastern population. This study aims at assessing the prevalence and reclassification potential of VUS in a cohort of Levantine patients at risk of HBOC.

Methods: A retrospective chart review of patients at risk of HBOC tested at the American University of Beirut Medical Center between years 2010 and 2019 was conducted. Genetic testing results, as well as epidemiological, clinical and pathology data were extracted for 347 patients. Review and reclassification of VUS were performed according to the latest ACMG/AMP criteria and the ClinGen ENIGMA methodology. Data were analyzed in SPSS v29 using Chi-square and one way ANOVA tests, with $p \leq 0.05$ as significant. Significant results were reviewed for confounders using multivariate regression.

Results: 160 genomic alterations classified as VUS were detected. Of those, 32.5% were reclassified, including 4 variants upgraded to pathogenic/likely pathogenic. Non-informative results were present in 40% of participants, with a median of 4 total VUS per patient (mean ACMG pathogenicity score: 3.77). VUS carriers were more likely to have a personal history of breast cancer (72%), specifically triple negative breast cancer (19%).

Conclusion: These findings reveal a high burden of non-informative variants in our population, yet lack of external and functional validation limit the generalizability of our study. Improved genetic diversity in reference datasets and regionally adapted classification strategies are required.

Keywords: hereditary breast and ovarian cancer, variants of uncertain significance, BRCA1, BRCA2, Middle East, variant classification

Introduction

Genetic testing for Hereditary Breast and Ovarian Cancer (HBOC) has undergone significant evolution since the identification of the *BRCA1* and *BRCA2* genes in the early 1990s. The discovery of numerous causative genes and the democratization of genetic sequencing technologies have led to the implementation of extensive gene panels for HBOC. This shift has broadened the scope from "BRCA1/2 testing" to "hereditary cancer testing", as noted in the National Comprehensive Cancer Network (NCCN) guidelines.[1] The introduction of additional cancer-related genes in testing panels led to an increase in the number of detected variants, including Variants of Uncertain Significance (VUS).

In clinical settings, the criteria for genetic testing are primarily derived from studies involving participants of European descent.[2,3] Additionally, the interpretation of sequencing results relies on variant frequency, which is extrapolated from population databases frequently lacking sufficient representation from diverse populations (Genome Aggregation Database; https://gnomad.broadinstitute.org). Consequently, genetic testing results of patients with diverse global backgrounds tend to show a lower fraction of pathogenic variants and a higher proportion of VUS, as demonstrated across different ethnic groups in the United States.[3] In a studied population of breast cancer patients, Asian and

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Hispanics individuals presented the highest rate of VUS (21.9% and 19% respectively), with 17.1% of Black patients carrying an unclassified variant.[4]

The disclosure of uncertain results exacerbates the psychological burden associated with genetic testing. Ambiguous testing results were shown to be associated with negative patients' reactions, including over-interpretation, anxiety, frustration, hopelessness, and decisional regret.[5] Misinterpretation of VUS as pathogenic or benign variants is also common, resulting in erroneous expectations of their clinical impact.[5] Studies also show that participants with uncertain results have a higher difficulty understanding and recalling the outcome of their genetic tests.[6–9] Negative reactions are particularly prevalent in breast cancer patients, possibly due to heightened anxiety about the disease, uncertainty in decision-making regarding treatment or prophylactic surgery, and the emotional burden of hereditary risks.[10] Patients reported as well their concerns from the possibility of detecting unsolicited findings, adding further responsibility on genetic counselors to provide patients with a comprehensive educational and emotional support.[11]

Ethnic differences in VUS constitute a major challenge for laboratory geneticists, counselors, and primary care physicians practicing in data-limited regions. As physicians from the Middle Eastern region, we noticed that our patients frequently receive uncertain results. The proportion of informative (pathogenic and benign) and non-informative (VUS) genetic testing has not yet been assessed in the Levant area, particularly for multigene HBOC testing.

Variant reclassification can significantly impact patients, affecting the clinical management in up to 41.3% of patients.[12] This concern has driven global efforts in the aim of enhancing variant classification guidelines. The ClinGen ENIGMA expert panel recently published a BRCA1/BRCA2 track set resulting in a dramatic reduction of VUS compared to the standard ACMG/AMP classification system.[13]

In this study, we aim at determining the prevalence of non-informative results in a Levantine, Lebanese based, cohort of patients at high risk of HBOC. The demographic and clinical characteristics of VUS carriers are assessed and compared to patients with informative genetic testing results.

Materials and Methods

Study Design and Population

In this retrospective study, the germline genetic testing results of adult subjects at risk of HBOC were retrieved from the Electronic Health Records of the American University of Beirut Medical Center (AUBMC), Lebanon between January12010and August 31 2019. Patients were referred for testing by medical oncologists, surgical oncologists, and/or genetic counselors at our institution if they met the clinical testing criteria of the NCCN guidelines.[1] Patients not meeting the NCCN, or American College of Medical Genetics and Genomics (ACMG)[2] criteria were excluded from this study. Individuals referred for targeted testing of a known familial variant were also not included. A retrospective chart review was conducted to collect epidemiological (age, gender), clinical (personal and family medical and surgical history, type of cancer, disease stage, and outcome at last follow-up), and pathology/immunohistochemistry data (ER, PR, Her2, and Ki-67%). Disease staging was determined as per the American Joint Committee on Cancer (AJCC).[14] Outcome at last follow-up was selected from the following criteria: alive with no evidence of disease, alive with disease, alive unknown disease status, dead of disease, dead of other causes, dead unknown cause, and lost to follow-up. Cutoffs for immunostains were based on the College of American Pathologists guidelines.[15]

Ethical Considerations

This study was approved by the Institutional Review Board at the American University of Beirut.

Genetic Testing

From January 1, 2010 to January 1, 2015, genetic testing was limited to in-house Sanger sequencing of the *BRCA1* and *BRCA2* genes, covering all coding exons and immediately flanking intronic regions. From 2015 and inward, Next Generation Sequencing (NGS) panels outsourced to Centogene (CentoCancer®)[16] and Genekor (HerediGENE®)[17] laboratories, were implemented. Across platforms, patients with non-informative or negative results received reflex testing using Multiplex Ligation-dependent Probe Amplification (MLPA) for the detection of large deletions/duplications.

Variant Reclassification

Reported germline variants (Class 3, 4 and 5) were reviewed by two independent assessors (one certified laboratory geneticist, and a laboratory scientist experienced in variant classification). The reclassification process was based on the ACMG/AMP 2015 criteria and the ClinGen ENIGMA methodology for the reclassification of *BRCA1* and *BRCA2* variants.[18,19] Determination of variant frequency relied on the Genome Aggregation Database (gnomAD v2.1.1) database. Variants were assessed by in-silico predictors Variant Effect Predictor (VEP-Ensembl, release 114), Polyphen and SIFT. The peer-reported evidence for each variant was consulted in ClinVar archives. Nucleotide conservation prediction was based on the Phylo P computational scores. Reclassification data was combined from the two reviewers, after discussion and consensus on discrepant classifications.

The pathogenicity class of VUS (0–5) were reported as per the ACMG/AMP 2015 guidelines.[18]

Statistical Analysis

For the evaluation of the association between sequencing results, cancer history, and tumor characteristics, patient results were grouped into 3 categories: Pathogenic (including Pathogenic and Likely Pathogenic variants), VUS, and Negative (Benign/Likely benign). Statistical analysis was performed after variant reclassification using post-reclassification categories. The frequencies of demographic data were reported in means (± standard deviation) and percentages. Data were analyzed using the Chi-square test for categorical values and One-way Anova for the difference in means. A p-value ≤ 0.05 was chosen and adjusted as per the Bonferroni correction based on the number of tests (α_{adjusted}: 0.05/7= 0.007). Multivariate logistic regression was run to control for confounding in statistically significant variables. The analysis was conducted via the IBM SPSS statistics data editor version 29.

Results

Participants Characteristics

A total of 347 patients were included in this study, with a median age of 46 years (SD: 11 years). Females constituted the majority of the cohort (98%), 88% of whom were of Lebanese origin. Among tested individuals, 246 (71%) had a personal history of cancer, more commonly primary breast cancer (209/246; 85%). Remaining healthy participants (101/347; 29%) fulfilled familial history criteria for HBOC testing (Table 1).

Table 1 Participant Characteristics and Reason for Genetic Testing

Gender	
Female	340 (98%)
Male	7 (2%)
Country of origin	
Lebanon	305 (88%)
Iraq	27 (8%)
Syria	11 (3%)
Jordan	2 (0.6%)
Bahrain	1 (0.2%)
Sudan	1 (0.2%)

(*Continued*)

Table 1 (Continued).

Mean age (years)	
All	46
Female	46
Male	59
Reason for testing	
Breast cancer	210
Ovarian cancer	31
Breast and ovarian cancer	3
Metastatic prostate disease	1
Breast and prostate cancer	1
Family history	101

Variant Reclassification, Prevalence and Types

Before review and reclassification, 160 variants were reported as Class 3 (VUS). Reassessment based on population allele frequency, prediction algorithms, and published functional or clinical data allowed the reclassification of 52 variants (32.5%), of which 4 (2.5% of the total 160 VUS; Figure 1) were upgraded to Pathogenic/Likely Pathogenic (ACMG Classes 4 and 5). After review, 13% of tested patients (n=45) were determined as carriers of class 4/5 variants. Patients with reclassified pathogenic variants received genetic counseling to address risk assessment and tailored oncological surveillance, as per the NCCN guidelines. Targeted cascade testing was offered for family members. This highlights the clinical impact of VUS reclassification on HBOC patients' management. Remaining reclassified variants (48/160; 30%) were downgraded to Benign/Likely Benign (ACMG Classes 1 and 2) (Tables 2 and 3).

Interestingly, at least one VUS was reported in 138 of the total 347 tested patients (40%), with a median of 4 different VUS carried by patient (range: 0–6). The mean ACMG pathogenicity score of non-reclassified VUS, derived from a weighted combination of evidence categories defined by the ACMG/AMP guidelines, was 3.77. Of the 108 non-reclassified variants, 79 (73%) were absent from consulted large population databases, and 50 (46%) had no entry on ClinVar. VUS were more frequent in the *BRCA1, BRCA2, APC, POLD1*, and *POLE* genes.

Clinical Characteristics of VUS Carriers

There was no statistically significant difference in the mean age of patients with Pathogenic, VUS, and Negative results (p=0.128). Similarly, testing results did not seem to impact clinical characteristics such as the presence of a family history, stage at diagnosis and status at last follow-up (mean follow-up time: 7 years; range: 1 to 13 years). However, patients harboring VUS were more likely to have a personal history of breast cancer (p=0.0036), specifically triple-negative breast cancer (TNBC) (p=0.005), compared to patients with negative genetic testing results (Table 4).

Discussion

Based on the Lebanese National Cancer Registry database, breast cancer in Lebanese women is characterized by a younger onset and significantly higher age-specific incidence rates in groups below 50 years of age.[20] In our cohort of Levantine, majorly Lebanese patients, the proportion of pathogenic variants (13%) was found to be higher than what is typically reported in Western patients qualifying for genetic testing,[21–23] but comparable to groups with elevated pre-testing scores.[21] While the high prevalence of pathogenic variants in Arabs was previously reported, suggesting a distinct

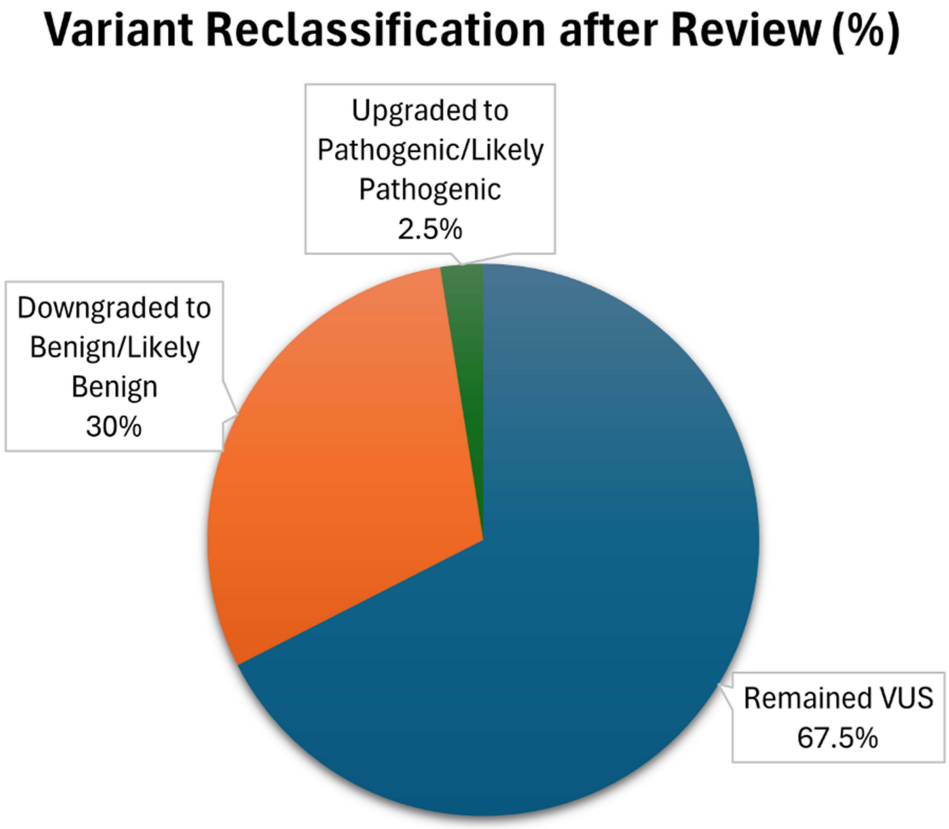

Figure 1 Outcome of variant reclassification after review by percentage.

biology of this ethnic group,[24] limitations of awareness and access to genetic testing might result in preferential testing of patients with markedly increased risks.

Our results show that among participants meeting the eligibility criteria for HBOC testing, 40% received non-informative results, with an average of ~4 total VUS/patient. This proportion is significantly higher than the 12.2% to 28.3% range described in Whites.[1,2] Prior studies have linked higher VUS prevalence to specific ethnicities, particularly Asians and other non-White groups.[21,22,24–28] Although the integration of machine learning technologies and predictive

Table 2 Genetic Location of Reviewed Variants of Uncertain Significance and Their Reclassification

	Before Review	After Review		
	Number of Variants Classified as VUS*	Number of Variants Classified as VUS*	Number of Variants Classified as Benign/Likely Benign	Number of Variants Classified as Pathogenic/Likely Pathogenic
BRCA1 exonic	18	10	7	1
BRCA1 intronic	28	20	7	1
BRCA2 exonic	13	8	4	1
BRCA2 intronic	35	25	10	
Non BRCA1/2 genes	66	45	20	1
Total	160	108	48	4

Notes: *VUS: Variants of Uncertain Significance.

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Table 3 Reclassified Variants of Uncertain Significance

Variant Nucleotide	Protein	Molecular Consequence	Reclassification	ACMG/AMP Criteria
BRCA1:c.2217dup	p.Val740fs	Frameshift	Pathogenic	PVS1,PM2,PP5
BRCA1:c.65_66delTA	p.Leu22Ter	Nonsense	Pathogenic	PVS1,PM2
BRCA2:c.8377G>A	p.Gly2793Arg	Missense	Likely Pathogenic	PM1,PM2,PP3,PP5
CHEK2:c.592+3A>T		Intron variant	Likely Pathogenic	PVS1,PM2,PS4,PP5
BRCA1:c.536A>G	p.Tyr179Cys	Missense	Likely Benign	PM1,PM2,BS1,BP4,BP6
BRCA1:c.1458T>G	p.Phe486Leu	Missense	Likely Benign	PM1,PM2,BS1,BP4,BP6
BRCA1:c.1648A>C	p.Asn550His	Missense	Benign	PM1,PM2,BS1,BS3,BS4,BP4,BP6
BRCA1:c.1703C>T	p.Pro568Leu	Missense	Benign	PM1,PM2,BS1,BS3,BS4,BP4,BP6
BRCA1:c.4132G>A	p.Val1378Ile	Missense	Benign	PM1,PM2,BS1,BS3,BS4,BP4,BP6
BRCA1:c.4985T>C	p.Phe1662Ser	Missense	Benign	PM1,PM2,BS1,BS3,BS4,BP4,BP6
BRCA1:c.2584A>G	p.Lys862Glu	Missense	Benign	PM1,PM2,BS1,BS3,BS4,BP4,BP6
BRCA1:c.5194–26 G >A		Intron variant	Benign	PM1,PM2,BS1,BS3,BS4,BP4,BP6
BRCA1:c.4357+117G>A		Intron variant	Benign	BA1, BP6
BRCA1:c.5711+36C>G		Intron variant	Benign	PM1,PM2,BS1,BS3,BS4,BP4,BP6
BRCA1:c.212+23T>A		Intron variant	Benign	BA1,BP6
BRCA1:c.301+55G>A		Intron variant	Benign	BA1,BP6
BRCA1:c.548–58delT		Intron variant	Benign	BA1,BP6
BRCA1:c.5406+68T>C		Intron variant	Benign	BA1,BP6
BRCA2:c.1385A>G	p.Glu462Gly	Missense	Benign	BA1,BP6
BRCA2:c.2803G>A	p.Asp935Asn	Missense	Likely Benign	PM1,PM2,BS1,BP4,BP6
BRCA2:c.3743G>A	p.Ser1248Asn	Missense	Likely Benign	PM1,PM2,BS1,BP4,BP6
BRCA2:c.6322C>T	p.Arg2108Cys	Missense	Benign	PM1,PM2,BS1,BS3,BS4,BP4,BP6
BRCA2:c.632–5T>C		Intron variant	Likely Benign	PM1,PM2,BS1,BP4,BP6
BRCA2:c.1910–74T>C		Intron variant	Benign	BA1,BP6
BRCA2:c.6938–120T>C		Intron variant	Benign	BA1,BP6
BRCA2:c.7008–62A>G		Intron variant	Benign	PM1,PM2,BS1,BS3,BS4,BP4,BP6
BRCA2:c.7435+53C>T		Intron variant	Benign	PM1,PM2,BS1,BS3,BS4,BP4,BP6
BRCA2:c.7806–14T>C		Intron variant	Benign	BA1,BP6
BRCA2:c.7976+23C>T		Intron variant	Benign	PM1,PM2,BS1,BS3,BS4,BP4,BP6
BRCA2:c.7976+35C>A		Intron variant	Likely Benign	PM2,BS4,BP6
BRCA2:c.8755–66T>C		Intron variant	Benign	BA1,BP6
BRCA2:c.9257–16T>C		Intron variant	Likely Benign	BP6,BP7
APC:c.3875C>T	p.Thr1292Met	Missense	Likely Benign	PM2,BS4,BP4

(*Continued*)

Table 3 (Continued).

Variant Nucleotide	Protein	Molecular Consequence	Reclassification	ACMG/AMP Criteria
APC:c.5026A>G	p.Arg1676Gly	Missense	Likely Benign	BS1,BP4,BP6
APC:c.6821C>T	p.Ala2274Val	Missense	Likely Benign	BS1,BP4
ATM:c.1810C>T	p.Pro604Ser	Missense	Benign	BA1
ATM:c.2634C>G	p.Thr878=	Synonymous	Likely Benign	BS1,BP6,BP7
BARD1:c.1694G>A	p.Arg565His	Missense	Likely Benign	BS1,BP4
CDH1:c.671G>A	p.Arg224His	Missense	Benign	BS2,BP2
CHEK2:c.157T>A	p.Ser53Thr	Missense	Likely Benign	PM2,BP4,BS4,BP6
MUTYH:c.1174C>A	p.Leu406Met	Missense	Likely Benign	BS1,BP1
PALB2:c.833_834delTAinsAT	p.Leu278His	Missense	Benign	BS1,BS4
POLD1:c.455C>T	p.Ala152Val	Missense	Likely Benign	BS1,BP4
POLD1:c.773C>T	p.Thr258Met	Missense	Benign	BS1,BS2
POLD1:c.883G>A	p.Val295Met	Missense	Likely Benign	BS1,BP4
POLE:c.3851G>A	p.Arg1284Gln	Missense	Likely Benign	BS1,BP6
POLE:c.4645C>G	p.Pro1549Ala	Missense	Likely Benign	BS1,BP4
RAD51B:c.728A>G	p.Lys243Arg	Missense	Likely Benign	PP3,BP4,BP6
RAD51D:c.286G>A	p.Ala96Thr	Missense	Likely Benign	BS1,BP4
SDHAF2:c.7G>T	p.Val3Leu	Missense	Likely Benign	BS1,BP4
SDHB:c.423+20T>A		Intron variant	Likely Benign	BS1,BP4
STK11:c.1145A>G	p.Gln382Arg	Missense	Likely Benign	BP4,BS4,BP6

Table 4 Multivariate Regression Analysis of Clinical and Demographic Criteria Across Pathogenic, Variant of Uncertain Significance (VUS), and Negative Genetic Testing Results

	Negative	VUS	Pathogenic	Exp (B)	*P Value*	*95% CI for Exp (B)*
Age at testing, years (Mean ± SD)	47.47 ± 10.6	46.2 ±11.75	44.13 ± 10.77	0.999	0.963	0.97–1.029
Family history [a] (% yes)	66	70	93	1.19	0.06	0.75–1.89
Prior history of cancer (% yes)	67	78	79	2.14	0.046	0.58–7.9
Personal history of breast cancer (% yes)	56	72	71	1.7	0.0036†	1.02–2.82
Triple negative (% yes)	10	19	20	1.06	0.005†	0.50–2.22
Late stage at diagnosis [b] (% yes)	12	11	17	21.45	0.727	0.01–42.8
Status at last follow up (% alive)	68	75	71	1.16	0.712	0.42–3.24

Notes: a. Family history is defined based on the NCCN guidelines for clinical testing. b. Late-stage breast cancer is defined as stages IIIB and IV. † α_Bonferroni corrected ≤ 0.007 (α ≤ 0.05), were considered statistically significant.

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algorithms helped reduce uncertain results,[29] these advancements have not benefited minority groups, where VUS rates continued to rise over time, exacerbated by the introduction of multigene panels in hereditary cancer testing.[22] Data on VUS prevalence and burden in the Arab and Middle Eastern populations remains limited. Consistent with our findings, Tatineni et al[24] reported that Arabs were twice as likely to carry a VUS compared to Whites and ranked second only to Asians among different racial groups. In a study of 39 breast cancer Moroccan women and a strong family history, Tazzite et al[25] identified 51 previously unclassified *BRCA1/2* variants. In contrast, a study among Jordanian patients reported a lower VUS prevalence of 9.2%.[27] This variation may be due to differences in testing criteria, variant interpretation, or sequencing methods. Notably, in that cohort, the use of multigene panels was found to raise the VUS rate to 22%.

Differences in implemented testing criteria, testing technologies, reanalysis time intervals and patient ethnicity create a wide range of VUS reclassification rates ranging from 3.6% to 58.8%.[12] Elevated reclassification rates of *BRCA1/2* variants were reported in Africans (42%), Middle Eastern (34.4%), and Chinese (33%) participants compared to other ethnicities like Hispanics (18.1%) and Asian non-Chinese (23.4%).[30] Recent advances in the availability of ethnic-specific population data helped increasing reclassification frequencies in HBOC patients, notably those of Black ancestry.[29]

Among non-BRCA genes, only one VUS in *CHEK2* was upgraded to likely pathogenic. *CHEK2* is known to be associated with a moderate increase in breast cancer risk, necessitating biannual screening by breast imaging. No known link to ovarian cancer has been established to date. The reclassification of VUS in the other non-BRCA genes to benign did not impact clinical management, as VUS are considered non-actionable in clinical practice.[31]

Peer-curated databases are predominantly based on European ancestry data entries,[32] and Middle Eastern individuals represent less than 0.1% of participants in large population databases (gnomAD v4.1.0).[33] As such, 50% of reviewed variants in our cohort lacked a ClinVar entry, and 73% were absent from consulted population databases, potentially limiting variant curation. This observation is further exacerbated by the limited access to functional and segregation studies in our region.

In our cohort, VUS carriers did not differ from patients with negative results regarding age, family history, staging, and clinical outcomes. The detection of VUS, however, may negatively impact patient management. Risks of over-treatment and heightened patient anxiety are exacerbated by a shortage of trained genetics professionals, financial barriers, and insufficient healthcare coverage. While data from US academic centers are reassuring,[34] limited data is available in our region on the clinical decisions made after the receipt of Class 3 results and warrant further investigation.[26,27]

Interestingly, patients with VUS were more likely to have a personal breast history of cancer, particularly TNBC. The association between VUS rates and a history of cancer is not well-established, yet several studies report a higher number of VUS in patients with prior cancer diagnosis.[28,29] Similarly, while the link between TNBC and *BRCA* pathogenic alterations is undebatable, the relation with VUS carriership is yet to be defined, with conflicting results in the literature.[27,35–37] It has been suggested that higher VUS prevalence in those patient groups is due to both higher baseline VUS prevalence and an underlying genomic instability.[25]

The study has set limitations. Its retrospective nature introduces a potential bias in the selection of patients for genetic testing, besides a small sample size for subgroups limiting further significant analysis. Moreover, despite the use of the standardized ACMG/AMP criteria for variant reclassification, we acknowledge that the absence of external validation by comparing to a second dataset or functional testing limits the generalizability of our results.

Conclusion

This study reveals a high burden of variants of uncertain significance in Middle Eastern patients undergoing HBOC testing, highlighting a critical gap in current genomic reference frameworks. Our results indicate a need to develop and adapt variant classification strategies given the potential impact on clinical management. Healthcare systems in the region must put efforts in facilitating access to genetic counseling and testing, and establish regional collaborations to enable ancestry-specific segregation and functional studies.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval Statement and Consent to Participate

This study received an approval from the Institutional Review Board at the American University of Beirut. A waiver of informed consent was granted from the Institutional Review Board at the American University of Beirut due to the retrospective nature of this chart review study, associated with minimal risk to participants. Patients' identification data was coded and the separate coding sheet linking the patient's identity to the code was available only for the principal investigator as a password protected soft copy on the PI computer. The study was conducted in full compliance with institutional ethical standards and in accordance with the principles of the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest.

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