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Original Article

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Multi-Gene Panel Testing for Hereditary Cancer Predisposition Among Patients Sixty-Five Years and Above Diagnosed With Breast Cancer

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Abstract

Background: The availability and affordability of germline genetic testing (GGT) has resulted in a broader utilization in daily clinical practice. However, adherence to testing guidelines is low, especially among older patients, where testing is often not offered.

Methods: In this study, consecutive, newly diagnosed patients with breast cancer (BC) aged ≥ 65 years and eligible for GGT, as per the National Comprehensive Cancer Network (NCCN) guidelines (version 1, 2021), were invited to participate, from March 2021 to December 2022. Patients were offered a restricted (two- or 20-gene panel), or an expanded 84-gene panel.

Results: During the study period, 204 patients were enrolled. The mean (standard deviation (SD)) age at BC diagnosis was 70.5 (5.13) years, ranging 65 - 81 years. All patients were Arab and the majority were Jordanian. The majority (n = 188, 92.2%) had early-stage (stages I and II) disease. One hundred three (50.5%) patients were tested with a restricted two-gene (n = 13) or 20-gene (n = 90) panel, while the remaining 101 (49.5%) patients had an expanded 84-gene panel. Family history of close blood relative(s) with BC was the most common indication for testing (n = 110, 53.9%). Among the entire study cohort, 22 (10.8%) had pathogenic/likely pathogenic germline variants (PGVs) and another 97 (47.5%) had ≥ 1 variants of uncertain significance (VUS). PGV rates were significantly higher with the expanded panel (14.9%) compared to restricted testing (6.8%) (P = 0.032). Similarly, VUS rates were significantly higher with the expanded panel (64.4%) compared to the restricted panel (31.1%) (P < 0.001). The most prevalent genes with PGVs were *BRCA1/2* (31.3% of all PGV-positive patients), *CHEK2* (23.1%) and *ATM* (19.2%).

Conclusion: GGT should not be overlooked in older BC patients, as this study demonstrates that > 10% of patients have PGVs, largely in potentially actionable genes.

Keywords: Germline genetic testing; Breast cancer; Predisposition genes; Older patients

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Introduction

Breast cancer (BC) is the most common cancer among women worldwide, the incidence of which increases with age; almost a third of all cases are diagnosed in patients older than 70 years [1]. The median age at diagnosis is 62 years in Western societies [2, 3], but 10 years younger in developing countries [4].

Though most BCs are sporadic, up to 20% of cases are familial and some are associated with pathogenic germline variants (PGVs) in cancer-predisposing genes [5, 6]. Some of these genes are highly penetrant, such as *BRCA1*, *BRCA2* and *PALB2* [7, 8], while others like *ATM* and *CHEK2* are associated with lower risks for cancer [9-11]. Hereditary BC is encountered more frequently in younger patients, those with positive family history, and those with triple-negative (TN) disease [12, 13].

Identifying carriers of such PGVs may help in cancer prevention through enhanced screening for breast and other cancers, and provide options for risk-reducing interventions like mastectomy and bilateral salpingo-oophorectomy (BSO) [14, 15]. However, the impact of PGVs in *BRCA1* or *BRCA2* has now moved beyond cancer prevention to involve treatment decisions of both early- and advanced-stage disease. The EMBRACA [16] and the OlympiAD [17] clinical trials have demonstrated that a poly (ADP-ribose) polymerase (PARP) inhibitor is superior to chemotherapy for *BRCA1/2* PGV carriers with advanced-stage, human epidermal growth factor receptor 2 (HER2)-negative BC. More recently, the OlympiA study has demonstrated significant improvement in outcomes, including

overall survival (OS), in patients with *BRCA1/2* PGVs who received PARP inhibitors in the adjuvant treatment of high-risk early-stage BC [18].

Several studies had shown that more than half of eligible patients with BC, as recommended by the National Comprehensive Cancer Network (NCCN) guidelines, never undergo germline genetic testing (GGT). Such underutilization is highest among minorities, underserved populations and older patients [19-22]. A study from the United Kingdom reviewed genetic counseling, referral and genetic testing of over 47,000 women. History of BC was identified in 2.7% of the cohort and 35.6% met one or more eligibility criteria for genetic testing; of these, 29.0% had a discussion with their healthcare provider, 20.2% were advised to undergo, and only 15.3% underwent genetic testing [23]. Other studies utilizing the Surveillance, Epidemiology, and End Results (SEER)-based databases from Seattle [24], California and Georgia [25] reached similar conclusions.

Current NCCN guidelines rely heavily on the patients' age at BC diagnosis with testing recommended for all BC patients diagnosed at age 50 or younger, regardless of their personal or family history of breast or other cancers, whereas older patients should have additional risk factors to be tested.

The aim of our study was to determine the prevalence of PGVs among Arab patients with BC diagnosed at age 65 years or older utilizing a multi-gene panel (MGP) of cancer-predisposing genes.

Materials and Methods

This was a prospective study of consecutive, newly diagnosed patients with BC aged 65 years or older and eligible for GGT, as per the NCCN guidelines. All patients were Arab, mostly Jordanians, diagnosed and treated at King Hussein Cancer Center, a comprehensive cancer center. Per patient choice, GGT was performed with a standard 20-gene guidelines-based or an expanded 84-gene panel testing. Prior to the availability of MGP testing, 13 patients were tested with *BRCA1* and *BRCA2* only. The 20-gene panel consists of *ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, NBN, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11* and *TP53*. Genes included in the 84-gene panel are detailed in Supplementary Material 1 (www.wjon.org).

DNA sequencing and analysis

Genetic testing was performed using a peripheral blood sample at two reference laboratories: Leeds Cancer Centre, St James's Institute of Oncology (Leeds, UK) for the *BRCA1* and *BRCA2*-only testing [12], and Invitae Corp. (San Francisco, USA) for the 20- and the 84-gene MGP testing. Whole gene sequencing, deletion, and duplication analysis of all coding exons, +/- 20 base pairs of flanking introns, and other special targets, and variant interpretations were performed at Invitae as previously described [26]. Variants were classified as negative, pathogenic/likely pathogenic (positive) and variant of uncertain significance (VUS). Demographics and clinical history were collected and analyzed from patients' electronic medical records.

Statistical analysis

Frequencies of pathogenic variants in each gene were assessed for patients with BC and stratified by gene panel used (restricted versus expanded), age group (≤ 70 versus > 70 years), presence of family history, multiple BCs, and TN disease. Proportions were compared using Fisher's exact test and significance was set at $P < 0.05$. All analyses were performed utilizing version 9.4 of SAS software (SAS Institute Inc., Cary, NC).

This study was approved by the Institutional Review Board at King Hussein Cancer Center (protocol number 20 KHCC 202), and was conducted in compliance with the ethical standards of the institution on human subjects as well as with the Helsinki Declaration.

Results

Between March 2021 and December 2022, 204 eligible patients were enrolled. The mean (standard deviation (SD)) age at BC diagnosis was 70.5 (5.13) years, ranging 65 - 81 years; 45 (22.1%) were > 75 years. The majority (n = 188, 92.2%) had early-stage disease, 13 (6.4%) were male and 33 (16.2%) had TN disease. All patients were Arab and the majority were Jordanian. Family history of close blood relatives (first-, second- or third-degree) with BC was reported by 143 (70.1%); 110 (53.9%) had close relatives diagnosed at age 50 years or younger, which was the most common indication for GGT in our cohort (Table 1).

Patients were tested based on NCCN guidelines, 103 (50.5%) were tested with restricted panels, *BRCA1* and *BRCA2* only (n = 13, 6.4%) or a 20-gene panel (n = 90, 44.1%), while the remaining 101 (49.5%) patients were tested using an expanded 84-gene panel. Among the entire study cohort, 22 (10.8%) had PGVs and 97 (47.5%) had VUS results in the absence of a PGV finding. PGVs were detected among seven (6.8%) patients who were tested using the restricted panels and among 15 (14.9%) patients who underwent the expanded 84-gene panel ($P = 0.032$). VUS rate was significantly higher in the expanded 84-gene panel (n = 65, 64.4%) compared to those who had restricted panel testing (n = 32, 31.1%, $P < 0.001$) (Fig. 1). One patient in the expanded-panel testing had increased risk allele (APC), two patients were carriers of *MUTYH* gene associated with autosomal recessive cancer risk and were excluded from the analysis. Among the 13 male patients included in the study, three (23.1%) had PGVs, all in *BRCA2.*

PGV rates were similar in patients ≤ 70 years (8.8%) and in those > 70 (12.7%) ($P = 0.18$). Additionally, we did not observe a significant difference in the prevalence of PGVs in patients with TN disease (9.1%) compared to other subtypes (11.1%) ($P = 0.37$). Family history of breast, ovarian, pancreatic, or prostate cancers was not associated with higher rates of PGV as detailed in Table 2.

PGVs were most frequent in *BRCA1/2* (31.3%), *CHEK2*

Table 1. Patients' Characteristics (n = 204)

Characteristics	Number	%
Age at diagnosis (years)		
Median (range)	70.5	
65 - 70	102	50.0%
71 - 75	57	27.9%
> 75	45	22.1%
Stage		
Early-stage	188	92.2%
Advanced-stage	16	7.8%
Hormonal status		
ER-positive	155	75.9%
PR-positive	148	72.5%
HER2 status		
HER2-positive	31	15.2%
HER2-negative	165	80.9%
Unknown	8	3.9%
Triple-negative		
Yes	33	16.2%
No	171	83.8%
Positive family history[a]		
Breast	143	70.1%
Ovarian, pancreas, high-grade prostate	34	16.7%
Nationality		
Jordanians	192	94.1%
Non-Jordanians	12	5.9%

[a]First, second or third-degree. ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2.

(23.1%), *ATM* (19.2%), and *APC* I1307K (11.5%) (Fig. 2). Detailed PGV findings are reported in Supplementary Material 2 (www.wjon.org). Notably, all identified PGVs were in genes included on the 20-gene panel.

Discussion

The emphasis in testing guidelines on age at diagnosis as a predictor for carrying a PGV in a cancer-predisposing gene, is a barrier to the identification of actionable PGVs [27]. Age was moved in the NCCN guidelines from 40, to 45, and lately to 50 years, as a cutoff for GGT. However, in its most recent guidelines update, the American Society of Clinical Oncology (ASCO) and the American Society of Surgical Oncology, both raised the age to commence testing to 65 years [28, 29]. Additionally, the most recently updated NCCN guidelines recommend germline testing of any patient with BC, regardless of their age, if such test results can aid in systemic treatment decisions using newly approved drugs like the PARP inhibitors in both early- and advanced-stage disease [16-18]. Additionally, age was disregarded in patients with TN disease, multiple BCs (synchronous or metachronous), and in those with lobular pathology with personal or family history of diffuse gastric cancer [30]. However, the decision to offer GGT for older women is often based on the coexistence of other risk factors for carrying cancer-predisposing genes including Ashkenazi Jewish ancestry, positive family history, TN disease and those with multiple primary BCs.

When testing older patients, the pre-test counseling should include a discussion of the relatively lower likelihood of positive results, compared to younger patients. Additionally, counseling should address, in addition to screening and preventive measures, the therapeutic implications of a positive test. However, given the age of patients under discussion, and the potential existing comorbidities, such patients might not be candidates for PARP inhibitors, enrollment in clinical trials, or other interventions [16-18]. Age, existing comorbidities and life expectancy should be the main factors on how extensive screening or risk-reducing interventions should be recommended for such patients. Nevertheless, identification of PGVs allows for cascade testing of at-risk family members and potentially life-saving early detection and risk-reduction opportunities.

Our study showed a relatively high rate of moderate-risk PGVs such as *CHEK2* and *ATM*. Women with such PGVs can have lifetime risks of BC that exceed 20%, which justifies more careful surveillance with annual breast magnetic resonance imaging (MRI) [31]. Additionally, *CHEK2* PGVs are associated with an increased risk of colorectal cancer, and *ATM* PGVs may increase the risk of pancreatic cancer. However, the clinical utility of increased surveillance in older patients with moderate-risk PGVs warrants additional studies.

Our PGV rate was slightly higher than what had been reported in Western literature. Kurian et al utilized data from the Women's Health Initiative which enrolled 161,808 postmenopausal women aged 50 to 79 years at 40 US sites from 1993 through 1998 [32]. A nested case-control study of women who were diagnosed with invasive BC (cases, n = 2,195) or remained cancer-free (controls, n = 2,322) was performed. The median age at BC diagnosis was 73 years for case participants and 81 years for the control. GGT was performed using a 28-gene panel. PGVs were detected in 6.7% (95% confidence interval (CI): 5.7-7.9%) and in 4.0% (95% CI: 3.2-4.0%) ($P<0.001$), among the case participants and the control group, respectively. Only 30.8% of case participants and 20% of controls with *BRCA1/2* PGVs met the NCCN guidelines. Age, above or below 70 years, had no impact on the frequency of PGVs in *BRCA1/2* ($P=0.34$) or other BC-associated genes ($P=0.54$) [32].

In another case-control study that aimed to address the effect of age on the frequency of PGVs in women with BC diagnosed at age over 65 years, 26,707 women from population-based studies (51.5% with BC and 48.5% unaffected) were enrolled. All women were tested utilizing a 12-gene panel of established BC risk genes (*ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D*, and *TP53*). The frequency of PGVs among women older than 65 years was 3.2% for those with BC and 1.5% for controls. PGVs were most frequent in *BRCA2* and *PALB2* for those with BC, while *CHEK2 and ATM* PGVs were common among those with and without cancer. Similar to our data, the frequency of pathogenic variants was not different across age groups;

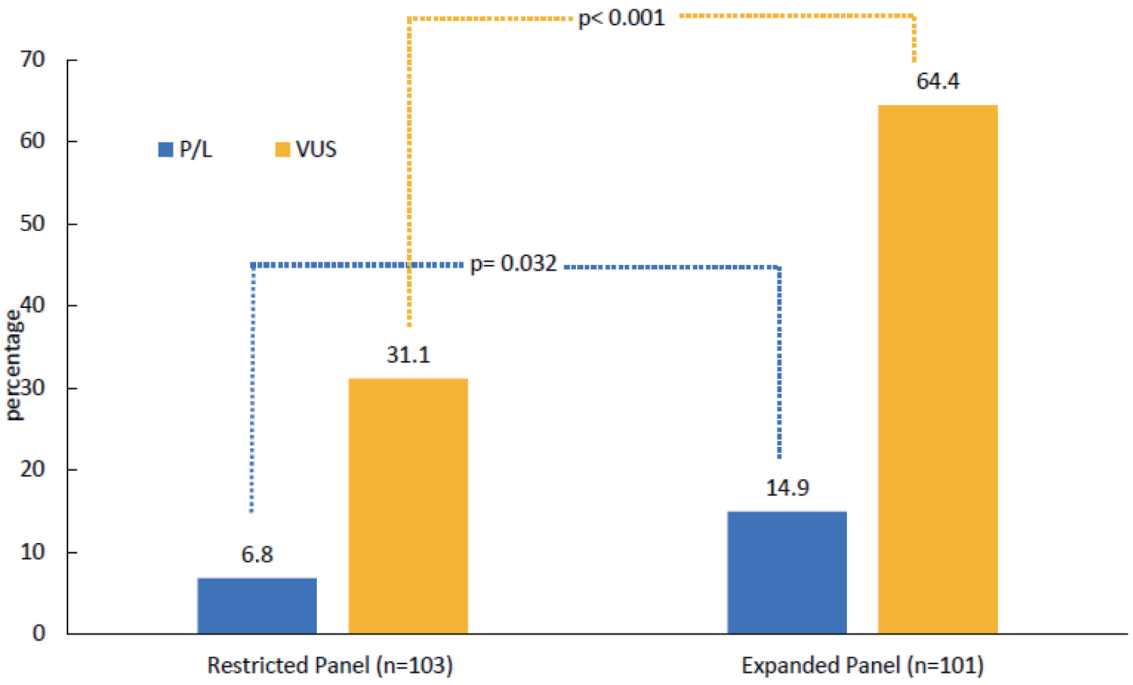

Figure 1. Results of germline genetic testing. One patient in the expanded-panel testing had increased risk allele (APC). Two carriers of autosomal recessive mutations were excluded. P/L: pathogenic/likely pathogenic; VUS: variants of uncertain significance.

women diagnosed at age (75 - 85) years and (66 - 75) years had similar rates for *BRCA2*, *CHEK2*, and *PALB2*. However, *BRCA1* was less common among the older subgroup [33].

Though the rate of pathogenic variants was higher in the group of patients tested with the expanded (84-gene) panel, most of the identified variants, except *APC* and *RAD50*, in the expanded panel were included within the restricted (20-gene) panel. As such, no real benefit of expanding the gene tested from 20- to 84-gene panel. On the other hand, such expansion may significantly increase the rate of VUS as illustrated in our study, from 31.1% to 64.4%. Such significant increase in the rate of VUS may increase patients' anxiety and add to the evolving pressure on health care systems to come up with appropriate plans to follow up on potential reclassifications of such variants. Given the ease of tailoring individual panel of gene tested, both *APC* and *RAD50* will be added to our BC gene panel for future testing.

Given the lack of accuracy of current testing guidelines, researchers are utilizing artificial intelligence and deep learning to better predict positive mutations based on distinct endophenotypes associated with different cancer predisposition genes in BC patients. Such a model achieved superior performance in identifying germline pathogenic variant carriers among Chinese BC patients in a recently published study [34]. More recently, our group reported our experience on universal testing of all cancer patients at diagnosis. Such argument is more convincing when considering BC [35].

Our study is not without limitations; the number of patients enrolled is relatively small, but that can be explained by demographics of Jordan population, with less than 5% of the population being > 65. Second, patients enrolled were from one center; however, given that the center treats over 50% of country's load of cancer cases, we believe the enrolled cohort is representable.

Conclusions

This study demonstrates that the rate of potentially actionable PGVs among older patients with BC is probably higher than that of Western societies, and is high enough to justify screening of eligible patients. Identification of PGVs can confer eligibility for targeted therapies and clinical trials, enhanced screening and risk-reducing interventions, and cascade testing of at-risk relatives.

Supplementary Material

Suppl 1. The 84-gene panel.

Suppl 2. List of all detected pathogenic/likely pathogenic variants.

Acknowledgments

None to declare.

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Table 2. Rates of Positive Pathogenic Variants by Indication

Variable	Total	Pathogenic/likely pathogenic mutations					
		All variants		*BRCA1/2*		Non-*BRCA1/2*	
		n (%)	P-value	n (%)	P-value	n (%)	P-value
Age at diagnosis (years)			0.18		0.23		0.29
≤ 70	102	9 (8.8%)		3 (2.9%)		6 (5.8%)	
> 70	102	13 (12.7%)		5 (4.9%)		8 (7.8%)	
Triple-negative disease			0.37		0.24		0.33
Yes	33	3 (9.1%)		2 (6.1%)		1 (3.0%)	
No	171	19 (11.1%)		11 (6.4%)		8 (4.7 %)	
≥ close blood relative with breast cancer diagnosed at age ≤ 50 years			0.47		0.17		0.21
Yes	110	12 (10.9%)		3 (2.7%)		9 (8.2%)	
No	94	10 (10.6%)		5 (5.3%)		5 (5.3%)	
≥ 1 close blood relative with: Epithelial ovarian cancer at any age; Exocrine pancreatic cancer at any age; Metastatic prostate cancer at any age			0.18		0.24		0.29
Yes	33	5 (15.2%)		2 (6.1%)		3 (9.1%)	
No	171	17 (9.9%)		6 (3.5%)		11 (6.4%)	
≥ 2 close relatives with breast cancer diagnosed at any age			0.38		0.39		0.27
Yes	86	10 (11.6%)		3 (3.5%)		7 (8.1%)	
No	118	12 (10.2%)		5 (4.2%)		7 (5.9%)	
More than one primary breast cancers, first diagnosed before age of 65 years			0.36		0.23		0.45
Yes	13	1 (7.7%)		0		1 (7.7%)	
No	191	21 (10.9%)		8 (4.2%)		13 (6.8%)	
Diagnosed at any age with a close male relative with breast cancer at any age			0.24		0.34		0.29
Yes	4	0		0		0	
No	200	22 (11%)		8 (4%)		14 (7%)	
All patients	204	22 (10.8%)		8 (3.9%)		14 (6.9%)	

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Conflict of Interest

Sarah M. Nielsen, Brandie Heald, Kathryn E. Hatchell and Edward D. Esplin, are (or were) employees at Invitae corporation, San Francisco, CA, USA. All other authors declared no competing interests.

Informed Consent

Written informed consent has been obtained from the all enrolled patients.

Author Contributions

Conceptualization: HAR and SMN. Data curation: FT, BS, KA, HBH, RM, AA, and MA. Formal analysis: HAR, FT, and HBH. Investigation: FT, BS, KA, HBH, RM, AA, and MA. Project administration: HAR, BS, and HBH. Supervision: HAR and HBH. Writing-original draft: HAR, FT, BS, SMN, BH, KEH, EDE, and HBH. Writing-review and editing: HAR, SMN, BH, KEH, and EDE.

Data Availability

The data supporting the findings of this study are available through the corresponding author upon reasonable request. All variants, including those reported in this manuscript, are

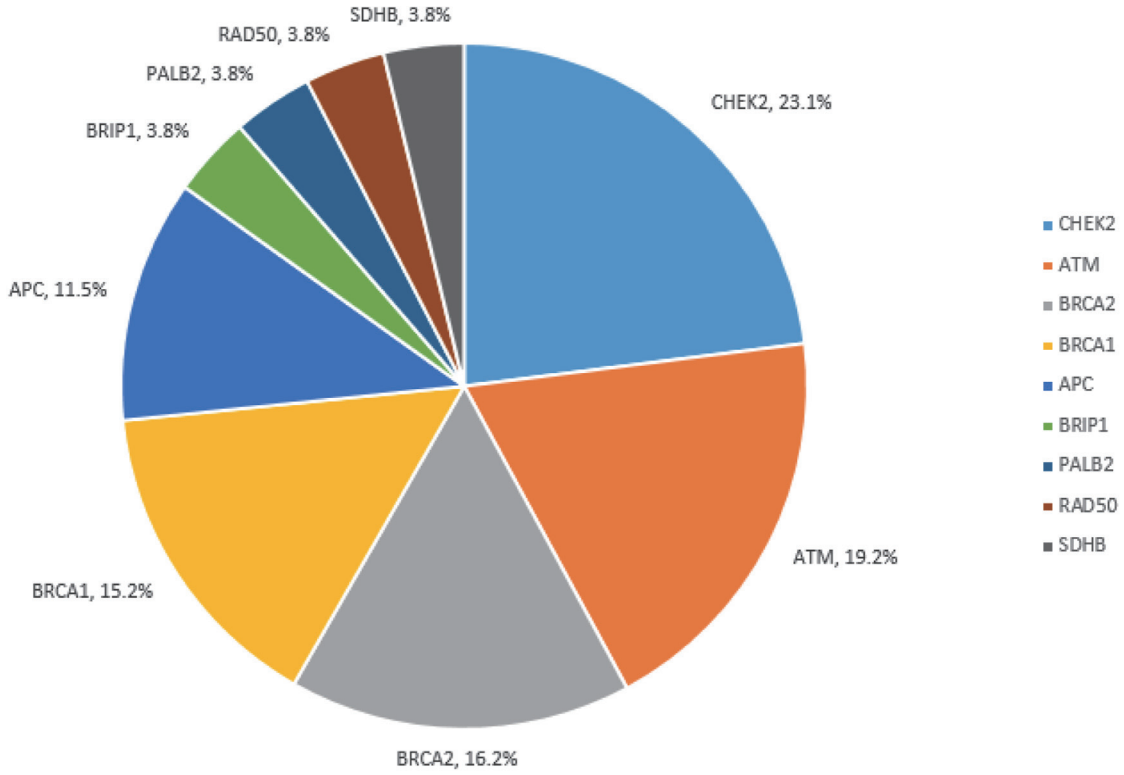

Figure 2. Pathogenic/likely pathogenic variants among all cohort.

submitted regularly to ClinVar. Our most recent submission has been processed in March 2023, which covered variants and interpretations to the end of 2022. Details are available at: https://www.ncbi.nlm.nih.gov/clinvar/submitters/500031

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