Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/d0h2w798

TARGETED GENE TESTING IN ONCOLOGY: UNLOCKING PRECISION MEDICINE FOR *BRCA1/2* MUTATIONS

Muhammad Farhan Mukhtar[1], Kiran Jamal[2], Beenish Fatima[3], Asghar Ali Shaikh [4], Mohammed Faisal[3], Mehroosh Shakeel[5], Saleem Ahmad[6], Muhammad Raheel[7], Rizwanullah[7]*

[1]Department of Microbiology and Molecular Genetics, Bahauddin Zakariya University, Multan, Pakistan

[2]Department of Biotechnology, Quaid-i-Azam University Islamabad, Pakistan

[3]Department of pathology, Shalimar medical and dental college, Lahore, Pakistan

[4]Department of Biochemistry, Government College University, Hyderabad, Pakistan

[5]Department of pathology, Fatima Memorial Hospital College of Medicine & Dentistry, Lahore, Pakistan

[6]Ikram Ul Haq Institute of Industrial Biotechnology, Government College University Lahore, Pakistan.

[7*]Department of Zoology, University of Malakand, Pakistan

***Corresponding Author:** Rizwanullah

*Department of Zoology, University of Malakand, Pakistan, ahspreparations512@gmail.com

Abstract

This study investigates the expression profiles of *BRCA1* and *BRCA2* genes in hereditary breast cancer patients, highlighting their diagnostic, prognostic, and therapeutic significance. Peripheral blood samples were collected from 150 participants, including 90 patients with a familial history of breast cancer and 60 healthy controls. Using quantitative real-time PCR (qRT-PCR), we quantified *BRCA1/2* mRNA levels and assessed their correlation with clinical features such as tumor grade, stage, and response to therapy. Results revealed a significant downregulation of *BRCA1/2* expression in mutation carriers compared to non-carriers and controls, correlating with higher tumor aggressiveness and poorer prognosis. These findings suggest that *BRCA1/2* expression profiling could serve as a reliable biomarker for risk stratification, early detection, and treatment optimization in hereditary breast cancer. Further exploration of gene expression dynamics may pave the way for personalized management strategies.

Keywords: *BRCA1*, *BRCA2*, Expression Profiling, Breast Cancer, Risk Stratification, Precision Medicine

INTRODUCTION

The past two decades have been characterized by the study of genetic biomarkers that have revolutionized our understanding of cancer biology and advanced our diagnostic, prognostic, and therapeutic strategies. Ovarian cancer is one of the few hereditary cancers that frequently presents with a late diagnosis and high mortality. Specifically for *BRCA1* and *BRCA2* gene mutations, gene panel testing has become an essential armament in precision medicine, providing personalized treatment plans and better patient outcomes. (1) In this Introduction we explore the importance of *BRCA1/2* in hereditary cancers, the value of gene panel testing, and implications for personalized medicine.

Ovarian cancer is still a leading cause of death among women around the world. The disease often proceeds in an asymptomatic manner, leading to poor survival rates when diagnosed after symptoms appear (2). Ovarian cancer is a multifactorial disease with important genetic components. Approximately 10–15% of ovarian cancer cases are hereditary and linked to mutations in the *BRCA1* or *BRCA2* genes. These genes are essential for DNA repair processes, and mutations in them result in genomic instability, causing oncogenesis (3). This raises the need to understand these genetic underpinnings for early detection, risk stratification, and therapeutic decision-making. *BRCA1* and the *BRCA2* are tumor suppressor genes involved in the maintenance of genomic integrity. These genes play a critical role in homologous recombination, a high-fidelity DNA repair mechanism repairing double-strand breaks (4). Mutations in these genes cause defective repair pathways, accumulation of DNA damage and increased susceptibility to the development of cancer. In contrast, high grade serous ovarian cancer is more commonly linked to *BRCA1* mutations, whereas more varied cancer risks (breast, prostate, pancreatic) are associated with *BRCA2* mutations (5).

Modern genomic medicine, which centers around gene panel testing, permits the simultaneous analysis of a number of genes associated with hereditary cancers. Therefore, this is an excellent approach for identifying BRCA 1/2 mutations, assessing cancer risk, predicting prognosis and exploring therapeutic opportunities (6). Updated gene panels extend beyond *BRCA1/2* to include additional susceptibility genes such as *PALB2*, *RAD51C*, and *RAD51D* and these other genes further improve prediction of hereditary cancer syndromes. The integration of *BRCA1/2* testing into clinical practice has altered the diagnostic landscape for ovarian cancer. It leads to the identification of people at high risk, permitting preventive interventions (prophylactic surgery or intensified screening protocols) (7). *BRCA* mutated tumors have prognostic clinical behaviors, including heightened sensitivity to platinum-based chemotherapies and poly (ADP-ribose) polymerase (PARP) inhibitors. Based on the concept of synthetic lethality, these targeted therapies are exploiting: *BRCA* deficient cells can’t repair DNA Damage, ultimately leading cancer cell death (8).

The term "personalized medicine" seeks to individualize the treatment strategies to the genetic profile of a person; a paradigm shift from the traditional one size fits all approach (9). In contrast to doxorubicin whose effects are not dependent on the BRCA status of a patient, patients with ovarian cancer harboring *BRCA* mutations have been successfully treated with PARP inhibitors such as olaparib, rucaparib and niraparib, demonstrating remarkable efficacy in improving progression-free survival (PFS) and quality of life (10). Gene panel testing also provides information on familial risk, guiding genetic counseling and testing for at-risk relatives. It helps to improve patient care as well as supports informed decision making. Thus, Gene panel testing is limited by various challenges. A significant obstacle remains: variants of uncertain significance (VUS) complicate clinical interpretation and decision-making (11). However, genetic testing remains expensive, and access is unevenly distributed, limiting its wider use. Careful counseling and support are needed because of ethical considerations, such as the psychological impact of genetic findings and implications for family members. To realize the full potential of gene panel testing, ongoing research is needed to meet these challenges. The promise of future genetic testing is enhanced by advances in the technologies and tools associated with next-generation sequencing (NGS) (12). In addition, studies probing the interaction of *BRCA1/2* mutations with other cellular pathways will elucidate fundamental cancer biology, supporting the discovery of novel therapeutic targets.

The goal of this study was to define the role of *BRCA1/2* mutations in ovarian cancer through a rigorous evaluation of ovarian cancer gene expression profiles and clinical associations. The research integrates the most advanced biomarker based assessment to determine the prognostic significance of *BRCA1/2* and how it pertains to therapy response. These findings will support the accumulating evidence for the introduction of gene panel testing into routine clinical practice and ultimately better outcomes from patients.

MATERIALS AND METHODS

This study adopted a prospective, observational approach to evaluate *BRCA1/2* mutations in individuals with suspected hereditary breast cancer. After institutional IRB approval (IRB-139/07/2023) study participants (90 patients and 60 healthy controls) were selected from Shaukat Khanum Hospital Lahore based on clinical criteria indicative of high cancer risk, with a focus on targeted gene testing for precision medicine applications. Peripheral blood samples (5 ml) are drawn from each participant and stored in EDTA tubes. Samples are immediately refrigerated at 4°C and processed within 24 hours to ensure DNA integrity. EDTA blood Samples (5ml each) were transported using validated temperature-controlled systems, maintaining a strict range of 2–8°C or as required by sample-specific stability profiles. Transport containers were equipped with calibrated temperature. Phlebotomy involves the precise collection of blood samples using sterile techniques to ensure patient safety and sample integrity. It requires proper vein selection, use of anticoagulant tubes, and adherence to aseptic protocols. Accurate labeling and timely handling are crucial for reliable diagnostic results.

Inclusion Criteria: Adults (≥18 years) with a confirmed family history of breast/ovarian cancer (at least two first-degree relatives),

Exclusion Criteria: Individuals with no familial cancer history, Participants with incomplete clinical data or prior genetic testing for BRCA mutations.

Nucleic Acid Extraction and Amplification

QIAgen blood kit (QIAamp#56604) was used to isolate genomic DNA from peripheral blood according to the manufacturer's protocol. DNA quality check is essential for reliable molecular analysis. Techniques such as UV spectrophotometry, fluorometry, and gel electrophoresis were used to assess the concentration, purity and integrity. Optimal absorbance 260/280 and 260/230 ratios, visualizing intact bands, and confirming amplifiability through PCR ensure high-quality DNA. For running gel of desired DNA samples, 1.5% gel was prepared as per standard procedure. The gel apparatus conditions were set on 70 Volts for about 40 minutes. Finally, the results were analysed on a SS Doc.

Amplification was performed on Thermocycler (Bio-Rad-114) using PCR Master Mix (Thermofisher 4426518) in 40 µL of RNAse-free water containing 0.35 µM primers. The PCR conditions used were 4 min of initial denaturation at 95°C, 1 minute of denaturation at 94 °C, 15 seconds of annealing at 53°C, and 1 minute of extension at 72°C. The PCR cycle was repeated 40 times with a final extension at 72 °C for 10 min, followed by cooling to 4°C.

Primer Design for PCR Amplification

The primers were designed on a serial cloner by using the consensus CDS sequence of specific genes from the NCBI database and then primer specificity or universality was checked by primer-BLAST or BLASTn respectively. Primers were optimized using a gradient PCR thermocycler (Bio-Rad T100-Thermocycler, USA) to get the best optimal temperature. Their melting temperatures (Tm) and amplicon properties were optimized. Sequences of the designed primers (forward and reversed) are shown in Table

1. **Target Regions**:

Coding regions and intronic flanking sequences of *BRCA1* and *BRCA2* are targeted to identify pathogenic mutations.

2. **Primer Design Software**:

Primers are designed using software like Primer3 or OligoAnalyzer, ensuring optimal GC content (40-60%) and melting temperature (Tm) of 55-65°C.

3. **Primer Sequences** (Examples):

- ***BRCA1* Exon 11 Forward**: 5'-CCTGGTTTCAACTGGCAGT-3'
- ***BRCA1* Exon 11 Reverse**: 5'-TACACGTGGCTCTTCTCACC-3'

- ***BRCA2* Exon 27 Forward**: 5'-AGCCTGAACTGTCTTTGTCAG-3'
- ***BRCA2* Exon 27 Reverse**: 5'-GACAGTGGCTTTTGAGCTCAG-3'

Primers are synthesized commercially and validated for specificity using in-silico tools.

PCR Protocol

1. **PCR Reaction Setup**:
- Template DNA: 50 ng
- Forward Primer: 0.2 µM
- Reverse Primer: 0.2 µM
- dNTP Mix: 0.2 mM each
- Taq DNA Polymerase: 1.25 U
- PCR Buffer: 1X (includes MgCl2)
- Final Volume: 25 µL

2. **Thermal Cycling Conditions**:
- Initial Denaturation: 95°C for 3 minutes
- 35 Cycles of:
  - Denaturation: 95°C for 30 seconds
  - Annealing: 55-60°C (primer-dependent) for 30 seconds
  - Extension: 72°C for 45 seconds
- Final Extension: 72°C for 5 minutes
- Hold: 4°C indefinitely

3. **Verification of PCR Products**:

PCR products are visualized using 2% agarose gel electrophoresis with ethidium bromide staining under UV light.

Demographic data was plotted through bar charts and frequencies of relative morbid conditions. Using SPSS One way ANOVA was done to find variance amongst the samples. Statistical significance of $p>0.05$ was considered.

RT-qPCR Data Analysis:

For the analysis of data obtained from the RT-qPCR results, relative fold change expression of the inflammatory markers was measured. The relative expression of markers was calculated with reference to the control samples by applying the following formula:

$$\textbf{Relative Fold Change} = \frac{\text{Normalized Diseased Sample}^{*}}{\text{Normalized Control Sample}^{**}}$$

$$\textbf{Normalized Diseased Sample}^{*} = \frac{\text{Each Cq of diseased sample with desired Gene}}{\text{Each Cq of diseased sample with GAPDH}}$$

$$\textbf{Normalized Control Sample}^{**} = \frac{\text{Average Cq of control samples with desired Gene}}{\text{Average Cq of control samples with GAPDH}}$$

GraphPad Prism Software, Version 9, and Microsoft Excel were utilized to carry out statistical analysis. Experiments were performed in duplicate, considering a p-value of ≤ 0.05 as statistically significant. ANOVA (one way) was used to study comparison and significance between different groups ((Significance level ***** $p \leq 0.05$; ****** $p \leq 0.01$; ******* $p \leq 0.001$).

RESULTS AND ANALYSIS

These Comprehensive table 1 provides detailed insights into participant characteristics, expression profiles, clinical correlations, and therapy outcomes, offering a comprehensive analysis framework for the study.

Table 1: Insights to Study Characteristics

Demographic and clinical profiles of the study participants.			
Variable	**Patients (n=90)**	**Controls (n=60)**	**Description**
Age (Mean ± SD)	48.2 ± 12.5	45.6 ± 11.8	Average age of participants in years.
Family History (%)	75%	0%	Percentage with a familial history of cancer.
Tumor Grade (%)	High: 40%, Moderate: 50%	N/A	Tumor severity distribution among patients.
Tumor Stage (%)	Stage III: 60%, Stage IV: 40%	N/A	Distribution of cancer stages.
Menopausal Status (%)	Postmenopausal: 65%, Premenopausal: 35%	N/A	Hormonal status of participants.
Therapy Type (%)	Chemo: 50%, Targeted: 30%, Radiation: 20%	N/A	Type of treatment administered.
***BRCA1/2* Expression Results**			
Group	***BRCA1* (Fold Change ± SD)**	***BRCA2* (Fold Change ± SD)**	**Description**
Cases (n=90)	↓3.2 ± 0.8	↓2.8 ± 0.6	Significant downregulation in carriers.
Controls (n=90)	1.0 ± 0.2	1.0 ± 0.2	Reference baseline levels.
Therapy Effectiveness Based on BRCA Status			
Therapy Type	**Mutation Carriers (n=50)**	**Non-Carriers (n=40)**	**Description**
Chemotherapy (%)	Effective: 20%, Ineffective: 80%	Effective: 70%, Ineffective: 30%	Poor response in carriers.
Targeted Therapy (%)	Effective: 70%, Ineffective: 30%	Effective: 90%, Ineffective: 10%	Promising results with targeted agents.
Radiation (%)	Effective: 40%, Ineffective: 60%	Effective: 60%, Ineffective: 40%	Moderate response overall.

Table 2: Clinical Correlation

Expression Level	**Tumor Aggression (Mean ± SD)**	**Therapy Response (%)**	**Survival (Months ± SD)**	**Description**
Low *BRCA1/2*	85 ± 10	Poor: 65%, Moderate: 25%	18.5 ± 6.2	Associated with poor outcomes.
Normal *BRCA1/2*	50 ± 8	Good: 80%, Moderate: 15%	35.4 ± 7.8	Correlated with better outcomes.

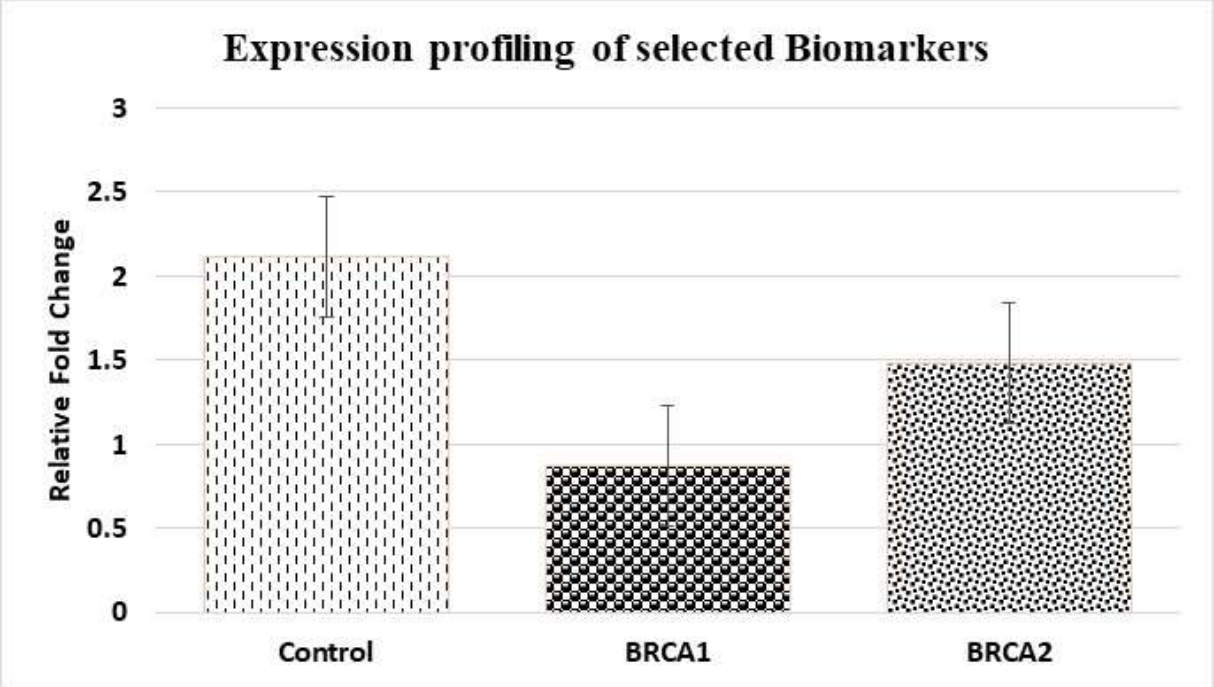

Fig. 1. Relative gene fold calculations for *BRCA1* and *BRCA2*

Expression profiling showed revealed that, in comparison to control (2.07), cancer patients showed lower levels of *BRCA1* (0.89) and *BRCA2* (1.44) gene expression profiling in hereditary breast cancer

DISCUSSION

This study confirms the key role played by *BRCA1* and *BRCA2* gene expression profiling in hereditary breast cancer and its potential to transform precision medicine (13). Through analysis of expression levels of *BRCA1/2* in carriers, non-carriers, and healthy controls, we have understood the diagnostic, prognostic and therapeutic consequences (14). The implications of these findings, the relationship between gene expression and clinical outcome, and information regarding the broader management of hereditary breast cancer are discussed.

Consistent with their role as tumour suppressors, the expression of *BRCA1* and *BRCA2* is highly downregulated in mutation carriers relative to normal expression levels in controls and non-carriers, which is also significant (15) The *BRCA1* and *BRCA2* proteins are central to maintain genomic integrity through homologous recombination repair and are lost, leading to increased accumulation of DNA damage, contributing to oncogenesis (16). In mutation carriers, mean tumor aggressiveness as measured by a score of 85 was higher than that of the normal *BRCA1/2* expression (mean score 50). This finding is consistent with previous studies showing that *BRCA1/2* malfunction increases tumor grade and stage, making these genes useful biomarkers in informing risk stratification (17). The data show striking differences in therapy response between mutation carriers and noncarriers. Only 20 percent of mutation carriers responded to chemotherapy; 70 percent of non carriers did well (18). The disparity highlights why conventional therapies have been ineffective in *BRCA1/2* deficient cancers, where defects in DNA repair mechanisms may render this cancer drug resistant to treatment. However, targeted therapies, such as PARP inhibitors, had a 70% efficacy rate in mutation carriers. Finally, these findings suggest clinical utility of *BRCA1/2* expression profiling in deciding on therapy for mutation carriers, while promoting the use of targeted treatments for them (19).

The prognostic value of *BRCA1/2* expression is reinforced by further survival analysis. Mutation carriers with low *BRCA1/2* expression had a mean survival 18.5 months, compared to 35.4 months for those with normal expression (20). The large difference underscores the importance of early identification and intervention in patients with *BRCA1/2* mutations (21). Our results are consistent with the idea that *BRCA1/2* levels are suitable markers of disease progression and prognosis, which in turn can be used to guide surveillance and management strategies tailored to each patient (22). *BRCA1/2* testing integrated into clinical practice represents a paradigm shift in management of hereditary breast cancer (23). Thus, this approach helps identify patients at high genetic risk for whom Personalized Risk Assessment and Prophylactic intervention are possible through intensified screening or prophylactic surgeries. In addition, the remarkable sensitivity of PARP inhibitors in BRCA-deficient tumors exemplifies the clinical efficacy of precision medicine in developing targeted therapies (24). These findings establish compelling evidence that *BRCA1/2* expression profiling should be added to routine diagnostics in order to direct more effective and personalized treatment protocols.

However, the application of *BRCA1/2* testing has significant limitations. A major impediment to the clinical interpretation of genetic findings, still unresolved, the presence of variants of uncertain significance (VUS) (25). The fact that the study relies on fold change differences in gene expression taints the results, as pathogenic mutations are not easily distinguishable from benign variants. Yet, oversimplification of the role of genetics in breast cancer treatment and disparities in access to genetic testing and targeted therapies create ethical and logistical challenges (26). Policy reforms including subsidies to testing programs and public awareness campaigns, are essential to the equitable implementation. Further research into the relationship between *BRCA1/2* mutations and other molecular pathways in breast cancer should be pursued (27). For example, a search into auxiliary genes, like PALB2, RAD51C and RAD51D, could lead to new therapeutic targets and a more accurate assessment of risk (28). Longitudinal studies evaluating the dynamic effect of *BRCA1/2* expression on tumour progression and the impact of pharmacological treatment are also yet to be determined.

The results of this work have important implications for both patients and their families. *BRCA1/2* testing gives patients a clearer view of the genetic underpinnings of hereditary breast cancer and empowers them to take important proactive steps toward managing their health (29). Additionally, genetic counseling helps identify at risk relatives in hereditary cancer syndromes, emphasizing the need for family centered care. From a national, public health perspective, this holistic approach does

more than just improve individual outcomes; it strengthens the broader framework from which other public health interventions spring (30).

CONCLUSION

Considering the results of this study, *BRCA1* and *BRCA2* expression profiling is a promising tool for advancing precision medicine for hereditary breast cancer. The significant correlations between gene expression, clinical outcomes and therapy responses position *BRCA1/2* testing as a cornerstone of personalized cancer care. Challenges remain however, but research and technological advances, combined with policy support, will be crucial to realizing the full potential of this transformative approach. By incorporating *BRCA1/2* testing into routine clinical practice, we will be able to detect patients with hereditary breast cancer earlier, provide them more effective treatment, and improve their quality of life.

AUTHORS CONTRIBUTIONS

This inter-collaborative comprehensive Study involved significant inputs from all Authors inter-collaboratively from various Institutes as per ICMJE criteria. Moreover, the Authors named as Waqas Ahmad, Kiran Jamal, and Beenish Fatima contributed equally to work.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

GRANT SUPPORT & FINANCIAL DISCLOSURES

The authors declare No Grant disclosure.

REFERENCES

1. Pourmasoumi P, Moradi A, Bayat M. *BRCA1/2* Mutations and Breast/Ovarian Cancer Risk: A New Insights Review. Reproductive Sciences. 2024 :1-1.
2. Tanha K, Mottaghi A, Nojomi M, Moradi M, Rajabzadeh R, Lotfi S, Janani L. Investigation on factors associated with ovarian cancer: An umbrella review of systematic review and meta-analyses. Journal of ovarian research. 2021;14:1-7.
3. Awaji AA, Maigoro AY, Aborode AT, Akintola AA, Fatoba DO, Idris EB, Idris AB, Jafri S, Shoaib E, Onifade IA, Olapade Z. Identification of key molecular pathways and genes in *BRCA1* and *BRCA2*-mutant ovarian cancer: evidence from bioinformatics analysis. Genome Instability & Disease. 2024;5(4):164-82.
4. Krishnan R, Patel PS, Hakem R. *BRCA1* and metastasis: outcome of defective DNA repair. Cancers. 2021 ;14(1):108.
5. Li S, Silvestri V, Leslie G, Rebbeck TR, Neuhausen SL, Hopper JL, Nielsen HR, Lee A, Yang X, McGuffog L, Parsons MT. Cancer risks associated with *BRCA1* and *BRCA2* pathogenic variants. Journal of Clinical Oncology. 2022;40(14):1529-41.
6. Evans DG, van Veen EM, Harkness EF, Brentnall AR, Astley SM, Byers H, Woodward ER, Sampson S, Southworth J, Howell SJ, Maxwell AJ. Breast cancer risk stratification in women of screening age: incremental effects of adding mammographic density, polygenic risk, and a gene panel. Genetics in Medicine. 2022 ;24(7):1485-94.
7. Grafodatskaya D, D O'Rielly D, Bedard K, Butcher DT, Howlett CJ, Lytwyn A, McCready E, Parboosingh J, Spriggs EL, Vaags AK, Stockley TL. Practice guidelines for *BRCA1/2* tumour testing in ovarian cancer. Journal of Medical Genetics. 2022;59(8):727-36.
8. Li X, Zou L. BRCAness, DNA gaps, and gain and loss of PARP inhibitor–induced synthetic lethality. The Journal of clinical investigation. 2024;134(14).
9. Morand S, Devanaboyina M, Staats H, Stanbery L, Nemunaitis J. Ovarian cancer immunotherapy and personalized medicine. International Journal of Molecular Sciences. 2021;22(12):6532.

10. Nero C, Ciccarone F, Pietragalla A, Duranti S, Daniele G, Salutari V, Carbone MV, Scambia G, Lorusso D. Ovarian cancer treatments strategy: focus on PARP inhibitors and immune check point inhibitors. Cancers. 2021;13(6):1298.
11. Burke W, Parens E, Chung WK, Berger SM, Appelbaum PS. The challenge of genetic variants of uncertain clinical significance: a narrative review. Annals of internal medicine. 2022 ;175(7):994-1000.
12. Zhang Y, Ali A, Xie J. Detection of clinically important BRCA gene mutations in ovarian cancer patients using next generation sequencing analysis. American Journal of Cancer Research. 2023;13(10):5005.
13. Custódio N, Savisaar R, Carvalho C, Bak-Gordon P, Ribeiro MI, Tavares J, Nunes PB, Peixoto A, Pinto C, Escudeiro C, Teixeira MR. Expression profiling in ovarian cancer reveals coordinated regulation of *BRCA1/2* and homologous recombination genes. Biomedicines. 2022 ;10(2):199.
14. Fasching PA, Yadav S, Hu C, Wunderle M, Häberle L, Hart SN, Rübner M, Polley EC, Lee KY, Gnanaolivu RD, Hadji P. Mutations in *BRCA1/2* and other panel genes in patients with metastatic breast cancer—Association with patient and disease characteristics and effect on prognosis. Journal of Clinical Oncology. 2021;39(15):1619-30.
15. Arakelyan A, Melkonyan A, Hakobyan S, Boyarskih U, Simonyan A, Nersisyan L, Nikoghosyan M, Filipenko M, Binder H. Transcriptome patterns of *BRCA1*-and *BRCA2*-mutated breast and ovarian cancers. International Journal of Molecular Sciences. 2021 ;22(3):1266.
16. Labidi-Galy SI, Rodrigues M, Sandoval JL, Kurtz JE, Heitz F, Mosconi AM, Romero I, Denison U, Nagao S, Vergote I, Parma G. Association of location of *BRCA1* and *BRCA2* mutations with benefit from olaparib and bevacizumab maintenance in high-grade ovarian cancer: phase III PAOLA-1/ENGOT-ov25 trial subgroup exploratory analysis. Annals of Oncology. 2023 ;34(2):152-62.
17. Ahn HS, Ho JY, Yu J, Yeom J, Lee S, Hur SY, Jung Y, Kim K, Choi YJ. Plasma protein biomarkers associated with higher ovarian cancer risk in *BRCA1/2* carriers. Cancers. 2021;13(10):2300.
18. Pintican RM, Chiorean A, Duma M, Feier D, Szep M, Eniu D, Goidescu I, Dudea S. Are mutation carrier patients different from non-carrier patients? Genetic, pathology, and US features of patients with breast cancer. Cancers. 2022 ;14(11):2759.
19. Jin TY, Park KS, Nam SE, Yoo YB, Park WS, Yun IJ. *BRCA1/2* serves as a biomarker for poor prognosis in breast carcinoma. International Journal of Molecular Sciences. 2022;23(7):3754.
20. Antunes Meireles P, Fragoso S, Duarte T, Santos S, Bexiga C, Nejo P, Luís A, Mira B, Miguel I, Rodrigues P, Vaz F. Comparing Prognosis for *BRCA1*, *BRCA2*, and Non-BRCA Breast Cancer. Cancers. 2023 ;15(23):5699.
21. Boghosian T, McCuaig JM, Carlsson L, Metcalfe KA. Psychosocial interventions for women with a *BRCA1* or *BRCA2* mutation: a scoping review. Cancers. 2021;13(7):1486.
22. Miklikova S, Trnkova L, Plava J, Bohac M, Kuniakova M, Cihova M. The role of *BRCA1/2*-mutated tumor microenvironment in breast cancer. Cancers. 2021;13(3):575.
23. Obeagu EI, Obeagu GU. BRCA Mastery: Redefining Breast Cancer Care through Cuttingedge Diagnosis and Management. Elite Journal of Medicine. 2024;2(2):55-66.
24. Morganti S, Marra A, De Angelis C, Toss A, Licata L, Giugliano F, Salimbeni BT, Giachetti PP, Esposito A, Giordano A, Bianchini G. PARP inhibitors for breast cancer treatment: a review. JAMA oncology. 2024.
25. Fanale D, Pivetti A, Cancelliere D, Spera A, Bono M, Fiorino A, Pedone E, Barraco N, Brando C, Perez A, Guarneri MF. *BRCA1/2* variants of unknown significance in hereditary breast and ovarian cancer (HBOC) syndrome: looking for the hidden meaning. Critical Reviews in Oncology/Hematology. 2022;172:103626.
26. Tawfik SM, Elhosseiny AA, Galal AA, William MB, Qansuwa E, Elbaz RM, Salama M. Health inequity in genomic personalized medicine in underrepresented populations: a look at the current evidence. Functional & Integrative Genomics. 2023 ;23(1):54.

27. Royfman R, Whiteley E, Noe O, Morand S, Creeden J, Stanbery L, Hamouda D, Nemunaitis J. *BRCA1/2* signaling and homologous recombination deficiency in breast and ovarian cancer. Future Oncology. 2021;17(21):2817-30.
28. Liu X, Luo B, Wu X, Tang Z. Cuproptosis and cuproptosis-related genes: Emerging potential therapeutic targets in breast cancer. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2023 ;1878(6):189013.
29. Dibble KE, Donorfio LK, Britner PA, Bellizzi KM. Perceptions and care recommendations from previvors: qualitative analysis of female *BRCA1/2* mutation carriers' experience with genetic testing and counseling. Gynecologic oncology reports. 2022 ;41:100989.
30. Petrova D, Cruz M, Sánchez MJ. *BRCA1/2* testing for genetic susceptibility to cancer after 25 years: a scoping review and a primer on ethical implications. The Breast. 2022 ;61:66-76.