Astana Medical Journal
e2790-1203

https://doi.org/10.54500/2790-1203-2025-6-125-amj005

Molecular-genetic profile of breast cancer: The role of BRCA mutations, germline and somatic alterations as a basis for personalized therapy

Ainur Samigatova [1], Aigul Saduakassova [2], Nursulu Altaeva [3], Kuantkan Zhabagin [4], Zhanar Zhakypbekkyzy [5], Timur Sarsengaliev [6], Almagul Zhabagina [7]

[1] PhD-student, Astana Medical University, Astana, Kazakhstan

[2] Head of the Center for Nuclear Medicine of the Medical Centre, Hospital of the President's Affairs Administration of the Republic of Kazakhstan, Astana, Kazakhstan

[3] Associate Professor, Head of the Department of Medical Genetics and Molecular Biology, Astana Medical University, Astana, Kazakhstan

[4] PhD, Senior Physician of the Center for Nuclear Medicine of the Medical Centre, Hospital of the President's Affairs Administration of the Republic of Kazakhstan, Astana, Kazakhstan

[5] PhD-student, Astana Medical University, Astana, Kazakhstan

[6] Head of the Department of Radioisotope Diagnostics of the Center for Nuclear Medicine of the Medical Centre, Hospital of the President's Affairs Administration of the Republic of Kazakhstan, Astana, Kazakhstan

[7] PhD, Radiologist, Astana Outpatient clinic №3, Astana, Kazakhstan

Received: 15.05.2025
Accepted: 10.07.2025
Published: 29.12.2025

*** Corresponding author:**
Ainur Samigatova,
E-mail:
ainur.samigatova86@gmail.com

Citation: Astana Medical Journal, 2025, 125 (6), amj005.

Abstract

Breast cancer remains one of the most prevalent and socially significant malignancies among women worldwide. Advances in molecular biology and oncogenetics have substantially transformed approaches to the diagnosis, prognosis, and treatment of breast cancer, with a growing emphasis on personalized medicine. This review explores the molecular-genetic landscape of breast cancer, focusing on the distinctions between germline and somatic mutations, their clinical relevance, and their role in guiding individualized therapeutic strategies. The results of the literature review demonstrated that germline mutations - particularly in *BRCA1* and *BRCA2* - are strongly associated with hereditary breast cancer predisposition, influencing both risk assessment and preventive strategies. In contrast, somatic mutations, including alterations in *TP53*, *PIK3CA*, and *ESR1*, play a pivotal role in tumor behavior, treatment resistance, and disease progression. Moreover, integrative molecular profiling using next generation sequencing incorporates both germline and somatic mutation data provides a more accurate framework for clinical decision-making in personalized therapy. Studies have shown that patients with combined profiling benefit from more precise therapeutic targeting, including *PARP*

inhibitors, endocrine therapies, and immune checkpoint inhibitors. The integration of germline and somatic analyses represents a critical step in the realization of precision medicine, ultimately improving therapeutic outcomes and prognosis in breast cancer patients.

Keywords: breast cancer, BRCA1/2, germline somatic mutation, next-generation sequencing, precision medicine.

1. Introduction

The relevance of breast cancer as a public health issue

Breast cancer (BC) continues to be one of the most common and socially impactful forms of malignant neoplasms among women globally, posing a significant challenge to public health systems. According to global epidemiological data from 2022, the total number of newly diagnosed cancer cases reached approximately 20 million, with cancer-related mortality approaching 10 million cases. Among these, BC ranks as the most frequently diagnosed cancer in women, accounting for more than 2.29 million new cases annually, making it the leading oncological pathology in the female population worldwide (1). A similar epidemiological pattern is observed in the Republic of Kazakhstan, where breast cancer accounted for 26.4% of all female malignancies in 2023, ranking first among cancers affecting women (2).

Understanding the molecular-genetic basis of breast cancer is essential for accurate diagnosis, optimal therapeutic decision-making, and outcome prediction in the context of personalized medicine. Genetic analysis in breast cancer typically involves the study of germline (inherited) and somatic (acquired) mutations. Determining which type of mutation should be prioritized for clinical evaluation necessitates a comprehensive approach that considers clinical objectives, therapeutic options, and the broader framework of personalized oncology.

Drawing on current data and evolving clinical demands in personalized breast cancer care, we hypothesize that an integrated molecular-genetic profiling approach - simultaneously assessing both germline and somatic mutations, particularly in patients with a hereditary predisposition - outperforms isolated analyses in optimizing diagnostic, prognostic, and therapeutic strategies. We suggest that such an integrative method, which accounts for both the tumor's genetic architecture and hereditary risk factors, will facilitate more accurate selection of targeted therapies, improve the prediction of treatment response, and enable more effective patient stratification for preventive measures and genetic counseling. This, in turn, may significantly enhance the clinical effectiveness of personalized management in breast cancer. Accordingly, this review consolidates current data on the molecular-genetic characteristics of breast cancer, with particular emphasis on the clinical implications of germline versus somatic mutations, aiming to support evidence-based decision-making in the era of precision medicine.

2. Materials and Methods

This study is based on the analysis of scientific publications published between 2015 and 2025, with the aim of systematizing modern data on the molecular genetic characteristics of breast cancer, especially in the context of the differences between germline and somatic mutations and their role in personalized medicine. The main sources of information were the leading international scientific databases: PubMed, Scopus and

Web of Science, Google Scholar (Fig. 1). The search strategy included the use of the following keywords and their combinations: "breast cancer", "BRCA1/2", "germline mutations", "somatic mutations", "next generation sequencing" (NGS), "precision medicine". Filters were applied to select peer-reviewed publications in English. At the initial stage of the analysis, 327 publications were identified that met the search criteria. After assessment of abstracts, study design and methodological quality, taking into account the relevance and clinical significance of the presented data, 36 articles that fully met the goals and objectives of this review were included in the final analysis. The selected publications were classified according to the following areas: genetic aspects of breast cancer: the contribution of hereditary and acquired mutations, the role of germline and somatic mutations in breast cancer carcinogenesis: from hereditary predisposition to molecular heterogeneity, the significance of next-generation sequencing (NGS) technologies: in diagnostics, prognosis and choice of therapy; clinical relevance of the integration of germline and somatic profiling in the framework of personalized medicine and genetic counseling. The analysis was carried out taking into account the latest recommendations of NCCN, ESMO, ASCO and other specialized communities. This approach allowed us to conduct a comprehensive review of current knowledge, identify current areas of scientific research and highlight the importance of comprehensive molecular genetic analysis in breast cancer in the era of precision medicine.

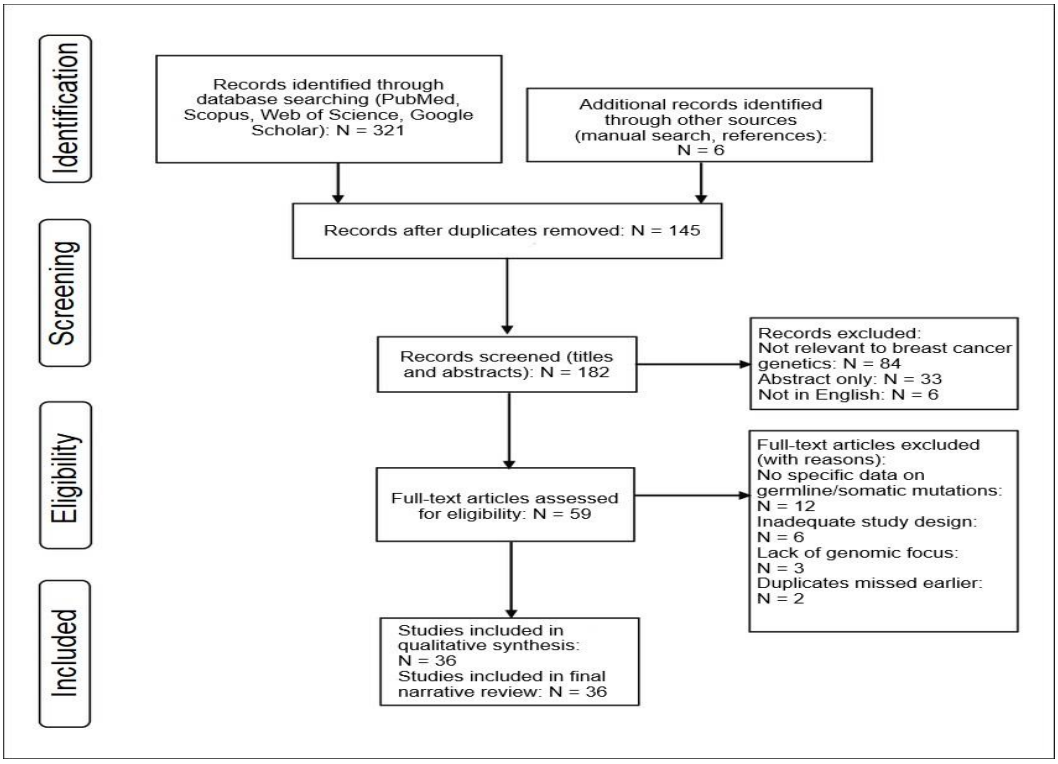

Figure 1 - Flow diagram

3. Results

The genetic nature of breast cancer: the role of germline and somatic mutations

Cancer is fundamentally a genetic disease, arising from alterations in genes that regulate cell growth and proliferation. These genetic aberrations may be inherited from parents (germline mutations) or may occur spontaneously during an individual's lifetime as a result of environmental and endogenous factors. Over

several decades, basic research has elucidated the mechanisms of cellular transformation and identified key driver mutations responsible for uncontrolled cell division and tumorigenesis (3).

In contemporary oncology, molecular-genetic profiling has become an integral component of comprehensive cancer diagnostics and therapy. Advances in molecular biology and cancer genetics have significantly expanded our ability to identify molecular biomarkers with substantial predictive and prognostic value. Genetic aberrations, particularly mutations, play a central role in oncogenesis. These mutations disrupt normal cellular functions, promoting unregulated proliferation, resistance to apoptosis, and metastatic potential (4). However, the identification of such mutations also offers a unique opportunity to distinguish malignant cells from normal tissues, which is critical for both diagnosis and the development of targeted therapeutic strategies. A profound understanding of the molecular and genetic mechanisms underlying malignancies, especially in the context of breast cancer (BC), forms the foundation for personalized molecular-targeted treatment approaches (5).

Genetic alterations associated with cancer can be transmitted through the germline and are responsible for approximately 5–10% of all breast cancer cases, significantly increasing the risk of malignancy. In breast cancer specifically, germline mutations, particularly in *BRCA1*/2 genes, play a pivotal role in the development of hereditary forms of the disease. In contrast, the majority of cases (90–95%) are considered sporadic, arising de novo and lacking familial inheritance patterns (6). Extensive studies of proto-oncogenes and tumor suppressor genes, as well as point mutations, have contributed significantly to our understanding of cancer pathogenesis. Proto-oncogenes, which normally regulate cell growth and differentiation, can become oncogenic through mutation or overexpression, resulting in loss of cell cycle control and malignant transformation. Conversely, tumor suppressor genes, which are responsible for cell cycle regulation and apoptosis, contribute to tumor development when inactivated or dysfunctional (7). The response of breast cancer patients to anti-cancer therapies is known to vary widely. This heterogeneity is driven by individual differences in the molecular pathogenesis of tumors, shaped by a diverse spectrum of driver gene mutations that initiate and sustain carcinogenesis. Studies of the molecular characteristics of breast tumors have revealed significant genetic heterogeneity and clonal evolution during disease progression. Elucidating the molecular profiles of tumor cells, particularly those associated with specific mutations, opens new avenues for improving therapeutic outcomes and survival (8).

Genetic testing can be applied in patients with a confirmed diagnosis of breast cancer to guide the selection of individualized targeted therapies. Furthermore, in patients under the age of 50 diagnosed with breast cancer, the identification of hereditary cancer syndromes can significantly influence both treatment and preventive strategies (9). Among unaffected individuals with a family history of cancer, the detection of germline predispositions allows for timely preventive interventions and early cancer detection. The variability in treatment response among patients is explained by molecular heterogeneity and the presence of diverse driver mutations, and their identification enables not only the discrimination of malignant from normal cells but also the rational application of precision-targeted therapies. Moreover, detecting either germline or somatic mutations facilitates the selection of specific targeted agents that directly interfere with aberrant signaling pathways driving tumor growth (10).

Therefore, given the molecular heterogeneity of breast cancer, modern approaches no longer prioritize either germline or somatic mutations in isolation. Instead, emphasis is placed on comprehensive molecular-genetic profiling. An integrative analysis of both mutation types - often utilizing next-generation sequencing (NGS) - provides the most complete representation of the tumor's genetic landscape and hereditary risk factors. This enables oncologists to make well-informed decisions that enhance diagnostic accuracy, optimize treatment strategies, and improve clinical outcomes for patients with breast cancer.

The role of germline mutations in the development of hereditary breast cancer

Hereditary cancer comprises a heterogeneous group of malignancies driven by germline mutations in one or more genes, inherited from a parent and present in all somatic cells of the body. These mutations typically affect genes critical for maintaining genomic stability, regulating the cell cycle, mediating DNA repair, or suppressing tumor development. In contrast to sporadic cancers, where mutations are acquired somatically during an individual's lifetime, germline mutations are inherited and often follow an autosomal dominant pattern, resulting in a 50% probability of transmission of the mutant allele to offspring. Although the presence of germline mutations significantly increases the risk of cancer development, it does not in itself guarantee tumor formation. This is explained by the concept of incomplete penetrance, which postulates that disease manifestation requires additional somatic mutations - the so-called "second hits" - that impair the function of the remaining wild-type allele or affect other tumor suppressor genes (11).

The most well-known and extensively studied genes implicated in hereditary breast cancer are *BRCA1* and *BRCA2*. Both are inherited in an autosomal dominant manner and play a key role in the homologous recombination repair of DNA double-strand breaks. Mutations in these genes disrupt the synthesis of functional proteins, leading to impaired DNA repair and accumulation of genetic damage that promotes malignant transformation (12). Carriers of *BRCA1*/2 mutations face a markedly increased lifetime risk of developing breast cancer. Moreover, *BRCA*-associated tumors are frequently characterized by a triple-negative molecular phenotype - lacking expression of estrogen receptors (ER), progesterone receptors (PR), and *HER2/neu* - which is associated with a more aggressive clinical course and limited options for targeted therapy. It has also been shown that mutation carriers tend to develop cancer at a younger age, which underlines the need for proactive clinical surveillance. Asymptomatic individuals with *BRCA1*/2 mutations should undergo regular monitoring and be considered for inclusion in personalized prevention and early detection programs (13).

Commonly identified pathogenic variants include *BRCA1 (185delAG, 5382ins*C) and *BRCA2 (617delT, 997del5)* mutations, which result in loss of gene function through frameshift-induced protein truncationгенов (14). Beyond *BRCA1*/2, several other genes have been implicated in hereditary breast cancer, including *MLH1, MSH2, TP53, CHEK2, PALB2, PTEN, NBN, ATM, BRIP1, RAD50, BLM*, and *FGFR2*, all of which are involved in cell cycle control, apoptosis, and DNA repair. This highlights the genetic heterogeneity underlying hereditary breast cancer syndromes. (15).

Accurate identification of germline mutations, along with assessment of their functional significance and population prevalence, is of critical importance for risk stratification, prognostic evaluation, and the selection of clinical management strategies. Given the high degree of molecular and clinical heterogeneity, the interpretation of mutational profiles necessitates an integrated approach involving molecular-genetic testing, genetic counseling, and personalized strategies for surveillance and therapy.

Somatic mutations and their role in carcinogenesis: molecular heterogeneity

Somatic mutations arise in post-zygotic somatic cells and, unlike germline mutations, are not heritable. These genetic alterations are confined to the affected cells and their clonal descendants, creating a genetic mosaicism within the organism. Although some somatic mutations are a consequence of physiological aging, their accumulation plays a critical role in the molecular pathogenesis of numerous diseases, particularly malignant neoplasms (16) .

It is now well established that somatic mutations constitute the genetic basis of the vast majority of sporadic cancers, which account for approximately 90% of all oncological cases. These mutations accumulate over a person's lifetime. While many are functionally neutral, a subset can disrupt critical cellular processes such as proliferation, apoptosis, and replication, thereby initiating oncogenesis. The principal molecular targets of somatic mutations in carcinogenesis are proto-oncogenes and tumor suppressor genes. When mutated, proto-

oncogenes can convert into oncogenes, acquiring the capacity to promote uncontrolled cell growth, invasion, and metastasis. One of the most studied oncogenes in breast cancer is *HER2/neu (ERBB2)*, a member of the epidermal growth factor receptor family. Its overexpression is associated with a poor prognosis and aggressive clinical behavior. Among the most frequently mutated genes in breast cancer, significant alterations are found in *TP53*, *PIK3CA*, *AKT1*, *GATA3*, *CDH1*, *MAP3K1*, *PTEN*, *ERBB2 (HER2)*, and *RB1* (17).

TP53 mutations are predominantly found in triple-negative breast cancers (TNBC) and are linked to a high level of genomic instability and malignant potential (18). In contrast, *PIK3CA* mutations are more common in hormone receptor-positive tumors (ER+/*HER2*−) and are generally associated with a favorable prognosis (19). CDH1 mutations result in the loss of E-cadherin function, impairing cell–cell adhesion and promoting invasive growth, particularly in lobular carcinoma. *ERBB2 (HER2)* amplification serves as a key biomarker for selecting patients for anti-*HER2* targeted therapies, including trastuzumab, pertuzumab, and T-DM1. *AKT1* mutations, such as *E17K*, activate the *PI3K/AKT* signaling pathway, conferring resistance to anti-estrogen therapy (20). Mutations in *MAP3K1* and *GATA3* frequently occur in luminal A/B subtypes and are generally associated with hormone receptor-positive phenotypes. Furthermore, *ESR1* mutations are most commonly observed in patients with metastatic or recurrent breast cancer who have previously received hormone therapy, particularly aromatase inhibitors. These mutations are rare in primary tumors, highlighting their acquired nature and possible selection under therapeutic pressure (21).

The immunogenic aspects of the somatic mutational profile also warrant attention - particularly *PD-L1* (programmed death-ligand 1) expression, which can be upregulated as a result of various somatic rearrangements and mutations (22). *PD-L1* expression is notably enriched in triple-negative breast cancers (TNBC), particularly those harboring *TP53* mutations, a high tumor mutational burden (TMB), and tumor-infiltrating lymphocytes (TILs) (23). Such tumors may be responsive to immune checkpoint inhibitors targeting *PD-1/PD-L1*, such as atezolizumab and pembrolizumab (24). Additionally, rare but clinically significant mutations in *MSH6*, *MLH1*, and *POLE*, associated with microsatellite instability (MSI) and a hypermutated phenotype, are also reported to confer enhanced immunotherapy sensitivity (25).

The detection and molecular characterization of somatic mutations are of paramount importance in modern oncology, particularly in breast cancer. These mutations are the driving force behind the majority of sporadic tumors and contribute to the genetic heterogeneity that underlies differences in tumor behavior, aggressiveness, and therapeutic response. Precise identification of somatic alterations - including driver mutations, gene amplifications, translocations, and immune-related markers such as *PD-L1* - enables patient stratification, disease prognostication, and the selection of individualized targeted and immunotherapies. As molecular diagnostic technologies rapidly evolve, the role of somatic mutation profiling continues to expand, becoming an indispensable element in the implementation of precision oncology.

Next-generation sequencing (NGS) in personalized breast cancer diagnostics

Contemporary molecular oncogenetics possesses a broad arsenal of highly sensitive and specific methods for detecting genetic alterations that play a pivotal role in oncogenesis. These methods enable the effective identification of both somatic mutations - occurring directly within tumor cells and serving as key drivers of malignant transformation - and germline mutations inherited from parents, which determine constitutional cancer predisposition (26). In routine clinical practice, somatic mutation analysis commonly relies on tumor tissue samples, most frequently formalin-fixed paraffin-embedded blocks obtained via biopsy or surgical resection. DNA extraction from these preserved samples permits subsequent sequencing or other molecular testing. In contrast, germline mutation detection is standardized through DNA analysis extracted from peripheral blood, since these mutations are present in all nucleated cells of the body. The application of advanced methods such as NGS enables comprehensive and high-throughput genomic profiling, allowing simultaneous analysis of numerous genes and

the detection of a wide mutation spectrum - an essential requirement for personalized oncology (27).

This technology, regarded as the "gold standard" in molecular diagnostics of malignancies, permits detailed examination of nucleotide sequences in both DNA and RNA, providing integrative predictive, prognostic, and diagnostic information necessary for personalized patient management (28). Unlike conventional molecular methods, NGS facilitates parallel sequencing of thousands of fragments, significantly accelerating genome decoding and enabling the detection of rare or low-frequency mutations.

At the international level, leading clinical guidelines - including those from NCCN, ESMO, and ASCO - now incorporate NGS into diagnostic and therapeutic algorithms for various cancers, including breast cancer (29). NGS is particularly valuable when triaging patients for targeted therapy. Large-scale studies have shown that NGS usage is associated with improved clinical outcomes: patients who underwent sequencing and received tumor profile - guided treatment demonstrated higher progression-free survival (PFS) and overall survival (OS) compared to those who did not receive molecular stratification. Например, в исследовании Kato et al. (2020) таргетированное лечение, основанное на результатах For example, in the study by Kato et al. (2020), targeted therapy based on NGS results and evaluated by a multidisciplinary tumor board resulted in statistically significant improvements in both PFS (HR = 0.63; 95% CI: 0.50–0.80; P < 0.001) and OS (HR = 0.67; 95% CI: 0.50–0.90; P = 0.007) (30).

Additionally, the size of the sequencing panel influences diagnostic yield. In the study by Kopetz et al. (2019), the use of an expanded NGS panel identified at least one previously undetected activating oncogene mutation in 41% of patients, of whom 19% received personalized therapy - associated with a significant improvement in overall survival (P = 0.017) (31). Similarly, the systematic review by Gibbs et al. (2023) demonstrated that in the majority of included publications, the application of NGS and targeted treatments led to improved clinical outcomes across various tumor types, including breast cancer (32).

Thus, whole-genome sequencing utilizing NGS technologies has become an indispensable component of modern oncogenetic diagnostics. It enables the detection of a broad spectrum of clinically relevant mutations and the assessment of immune target expression. Given the genetic heterogeneity of tumors - particularly in breast cancer - implementing NGS facilitates more accurate patient stratification, therapy response prediction, and treatment optimization. The integration of this technology into routine clinical practice significantly enhances the capabilities of personalized medicine and improves overall oncological treatment effectiveness.

Clinical significance of germline and somatic mutations in breast cancer

The identification of germline and somatic mutations in breast cancer holds substantial clinical importance and should be conducted in alignment with therapeutic goals, disease stage, and a personalized approach. In many cases, the detection of germline mutations - such as *BRCA1* and *BRCA2* - is essential at the time of initial diagnosis to assess hereditary cancer risk and to inform prophylactic or targeted interventions. However, as the disease progresses or therapy resistance develops, the clinical priority shifts toward re-evaluating the tumor's molecular profile to detect both *BRCA1*/2 and newly acquired somatic mutations, which reflect subclonal evolution and guide subsequent therapeutic decisions (33).

The crucial role of early germline *BRCA1*/2 mutation testing is underpinned by a combination of factors suggestive of hereditary predisposition. These include early-onset breast cancer, which significantly increases the likelihood of harboring pathogenic variants in predisposition genes (34). Special attention is given to patients with triple-negative breast cancer (TNBC) diagnosed at a young age, as this subtype is statistically more frequently associated with germline *BRCA1* mutations. A strong family history, including breast, ovarian, pancreatic, or prostate cancer in first-degree relatives, serves as a strong indicator for preventive genetic screening (35). Beyond individual clinical features, demographic and ethnic characteristics also play a critical role in determining the appropriateness of *BRCA1*/2 genetic testing. Due to the heterogeneity of

tumor biology and population-specific genetic variations, extended genetic screening is warranted in many countries - even in the absence of early-onset disease or a clear family history. The identification of *BRCA1*/2 mutation carriers not only allows for precise risk stratification of the index patient but also provides essential information for at-risk relatives, supporting cascade testing and the implementation of individualized surveillance and prophylactic strategies, including risk-reducing mastectomy and salpingo-oophorectomy (36).

In the context of metastatic disease and therapeutic resistance, the assessment of somatic mutations becomes paramount, complementing data on germline predisposition. Unlike inherited alterations, somatic mutations arise de novo in tumor cells during carcinogenesis and clonal evolution. These mutations are not heritable and reflect the specific molecular profile of a tumor at a given point in its progression. Modern approaches to the treatment of metastatic breast cancer increasingly rely on the principles of precision oncology, whereby therapeutic selection is contingent upon the identification of actionable driver mutations that dictate drug sensitivity or resistance. Comprehensive genomic profiling methods, such as next-generation sequencing (NGS), enable the detection of a wide range of clinically relevant somatic alterations in genes beyond *BRCA* - including PIK3CA, *ESR1*, *ERBB2*, *TP53*, and others - thus providing a foundation for treatment personalization (37).

As the disease advances or resistance emerges, dynamic monitoring of somatic mutations becomes an indispensable clinical tool. Under therapeutic pressure, tumors may acquire new mutations or exhibit clonal selection of pre-existing resistant subpopulations. In such scenarios, re-biopsy of tumor tissue - or increasingly, liquid biopsy via analysis of circulating tumor DNA (ctDNA) in plasma - enables real-time monitoring of molecular evolution. For example, *ESR1* mutations serve as biomarkers of resistance to endocrine therapy and may indicate the need for *CDK4/6* inhibitors or alternative treatments. Similarly, somatic mutations in DNA repair genes, such as *BRCA1*/2 or others involved in homologous recombination, may confer sensitivity to *PARP* inhibitors - even in the absence of inherited mutations - when acquired de novo in the tumor (38).

In summary, the comprehensive assessment of both germline and somatic mutations constitutes a cornerstone of modern oncology. Germline mutations inform hereditary risk assessment, guide familial testing strategies, and influence systemic treatment choices, including the use of *PARP* inhibitors in adjuvant and metastatic settings. Somatic mutations, by contrast, are critical for adapting treatment to the evolving molecular landscape of the tumor, particularly in the metastatic setting, where the timely identification of resistance mechanisms enables switching to more effective targeted therapies. The synthesis of data derived from both germline and somatic analyses facilitates the design of individualized treatment regimens tailored to the unique biological characteristics of each patient's tumor, ultimately improving therapeutic efficacy and clinical outcomes.

4. Discussion

The conducted literature analysis emphasized the important role of both germline and somatic mutations in the pathogenesis and clinical course of breast cancer. Particular attention is paid to mutations in the *BRCA1* and *BRCA2* genes, whose inherited pathogenic variants are associated with a high risk of breast cancer development and have a significant impact on the choice of therapy. Impaired mechanisms of DNA repair by homologous recombination caused by defects in these genes determines high sensitivity of tumors to *PARP* inhibitors and other agents inducing DNA damage. On the other hand, somatic mutations that occur sporadically during life significantly contribute to the molecular heterogeneity of breast cancer. In particular, variations in the *TP53*, *PIK3CA*, *AKT1*, *ESR1* and *GATA3* genes are associated with tumor aggressiveness, resistance to therapy and variability of the clinical course. These mutations can serve as both prognostic and

predictive biomarkers, especially when choosing targeted or hormonal drugs. The heterogeneity of somatic mutations necessitates molecular profiling of each tumor to justify the therapeutic strategy.

An integrated approach combining the analysis of germline and somatic changes using next-generation sequencing technologies has demonstrated high efficiency in the diagnosis and treatment of breast cancer. Integration of data on the patient's genetic background and tumor characteristics allows for more accurate risk stratification, determination of sensitivity to treatment, and prediction of outcomes. This is especially valuable for patients with a family history or "BRCAness" phenotype, in which tumors exhibit sensitivity to the same drugs as in BRCA-associated breast cancer, despite the absence of germline mutations.

At the same time, significant gaps in current knowledge have been identified. The interactions between different somatic mutations and their impact on clinical resistance, as well as the relationship between germline mutations in less studied genes (*PALB2*, *CHEK2*, *ATM*) and the molecular phenotype of the tumor, are insufficiently studied. The number of studies analyzing the combined effect of germline and somatic mutations on the choice of therapy, especially in the context of using combination treatment regimens, is limited. Approaches to interpreting variants of uncertain clinical significance are poorly developed, which complicates decision-making in clinical practice. The lack of uniform protocols for integrating NGS results into breast cancer treatment also remains an obstacle to the widespread implementation of precision medicine. Thus, the need for further research aimed at studying the interactions between different types of mutations and their clinical significance remains extremely relevant. This will improve genetic testing strategies, increase the accuracy of prognosis and move towards truly personalized treatment of breast cancer.

5. Conclusion

This review summarizes current knowledge on the molecular pathology of breast cancer, with a particular focus on germline and somatic mutations and an emphasis on the clinical relevance of *BRCA1* and *BRCA2*. Advances in molecular diagnostics have enabled the identification of oncogenic mutations not only in patients with breast cancer but also in healthy individuals, which is critically important for the personalization of diagnosis, treatment, and prevention strategies. The detection of *BRCA* mutations significantly enhances clinical disease management by informing the development of targeted therapeutic approaches and supporting genetic counseling and surveillance programs for mutation carriers. A clear distinction between germline mutations, which confer inherited predisposition, and somatic mutations, which act as drivers of sporadic tumor development, is of fundamental importance for understanding pathogenesis and selecting the appropriate clinical management strategy. Contemporary high-throughput sequencing technologies facilitate comprehensive analysis of both mutation types, forming the basis of personalized cancer care. An individualized approach to the assessment of both germline and somatic mutations is particularly valuable. In the presence of factors suggestive of hereditary cancer, comprehensive genetic testing - encompassing both inherited and acquired alterations - is advisable. Such an approach offers a more complete understanding of tumor biology and enables the optimization of therapeutic strategies tailored to the specific molecular features of each patient's disease.

Conflict of interest. The authors declare that they have no conflicts of interest.

Funding. No funding was provided.

Authors' contributions. Conceptualization – S.A., SA; methodology - A.N., Z.K.; validation - Z.A., S.T; formal analysis - S.A, A.N; writing (original draft preparation) - Z.Z.; writing (review and editing) - S.A, Z.K.

References

1. Bray, F., Laversanne, M., Sung, H., Ferlay, J., Siegel, R. L., Soerjomataram, I., Jemal, A. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, *74*(3), 229-263. https://doi.org/10.3322/caac.21834

2. Carbone, M., Arron, S. T., Beutler, B., Bononi, A., Cavenee, W., Cleaver, J. E., Yang, H. (2020). Tumour predisposition and cancer syndromes as models to study gene–environment interactions. *Nature Reviews Cancer*, *20*(9), 533-549. https://doi.org/10.1038/s41568-020-0265-y

3. Kontomanolis, E. N., Koutras, A., Syllaios, A., Schizas, D., Mastoraki, A., Garmpis, N., Fasoulakis, Z. (2020). Role of oncogenes and tumor-suppressor genes in carcinogenesis: a review. *Anticancer research*, *40*(11), 6009-6015. https://doi.org/10.21873/anticanres.14622

4. Feng, Y., Spezia, M., Huang, S., Yuan, C., Zeng, Z., Zhang, L., Ren, G. (2018). Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. *Genes & diseases*, *5*(2), 77-106. https://doi.org/10.1016/j.gendis.2018.05.001

5. Tempfer, C. B., Reymond, M. A. (2016). Sporadic cancers. In *The Molecular Basis of Human Cancer* (pp. 323-334). New York, NY: Springer New York. https://doi.org/10.1007/978-1-59745-458-2_21

6. Velez, A. M. A., Howard, M. S. (2015). Tumor-suppressor genes, cell cycle regulatory checkpoints, and the skin. *North American Journal of Medical Sciences*, *7*(5), 176. https://pmc.ncbi.nlm.nih.gov/articles/PMC4462812/

7. Xiong, X., Zheng, L. W., Ding, Y., Chen, Y. F., Cai, Y. W., Wang, L. P., Yu, K. D. (2025). Breast cancer: pathogenesis and treatments. *Signal transduction and targeted therapy*, *10*(1), 49. https://www.nature.com/articles/s41392-024-02108-4

9. Shah, R., Rosso, K., Nathanson, S. D. (2014). Pathogenesis, prevention, diagnosis and treatment of breast cancer. *World journal of clinical oncology*, *5*(3), 283. https://doi.org/10.5306/wjco.v5.i3.283

10. Santarpia, L., Bottai, G., Kelly, C. M., Győrffy, B., Székely, B., Pusztai, L. (2016). Deciphering and targeting oncogenic mutations and pathways in breast cancer. *The oncologist*, *21*(9), 1063-1078. https://doi.org/10.1634/theoncologist.2015-0369

11. Garutti, M., Foffano, L., Mazzeo, R., Michelotti, A., Da Ros, L., Viel, A., Puglisi, F. (2023). Hereditary cancer syndromes: a comprehensive review with a visual tool. *Genes*, *14*(5), 1025. https://doi.org/10.3390/genes14051025

12. Ismail, T., Alzneika, S., Riguene, E., Al-Maraghi, S., Alabdulrazzak, A., Al-Khal, N., Nomikos, M. (2024). BRCA1 and its vulnerable C-terminal BRCT domain: structure, function, genetic mutations and links to diagnosis and treatment of breast and ovarian cancer. *Pharmaceuticals*, *17*(3), 333. https://doi.org/10.3390/ph17030333

13. Paluch-Shimon, S., Cardoso, F., Sessa, C., Balmana, J., Cardoso, M. J., Gilbert, F., ESMO Guidelines Committee. (2016). Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. *Annals of Oncology*, *27*, v103-v110. https://doi.org/10.1093/annonc/mdw327

14. Abou-El-Naga, A., Shaban, A., Ghazy, H., Elsaid, A., Elshazli, R., Settin, A. (2018). Frequency of BRCA1 (185delAG and 5382insC) and BRCA2 (6174delT) mutations in Egyptian women with breast cancer compared to healthy controls. *Meta Gene*, *15*, 35-41. https://doi.org/10.1016/j.mgene.2017.11.002

15. Pal, M., Das, D., Pandey, M. (2024). Understanding genetic variations associated with familial breast cancer. *World Journal of Surgical Oncology*, *22*(1), 271. https://doi.org/10.1186/s12957-024-03553-9

16. Zhang, L., Vijg, J. (2018). Somatic mutagenesis in mammals and its implications for human disease and aging. *Annual review of genetics*, *52*(1), 397-419. https://doi.org/10.1146/annurev-genet-120417-031501

17. Beňačka, R., Szabóová, D., Guľašová, Z., Hertelyová, Z., Radoňák, J. (2022). Classic and new markers in diagnostics and classification of breast cancer. *Cancers*, *14*(21), 5444. https://www.mdpi.com/2072-6694/14/21/5444#

18. Mitri, Z. I., Abuhadra, N., Goodyear, S. M., Hobbs, E. A., Kaempf, A., Thompson, A. M., Moulder, S. L. (2022). Impact of TP53 mutations in triple negative breast cancer. *npj Precision Oncology*, *6*(1), 64. https://doi.org/10.1038/s41698-022-00303-6

19. Araki, K., Miyoshi, Y. (2018). Mechanism of resistance to endocrine therapy in breast cancer: the important role of PI3K/Akt/mTOR in estrogen receptor-positive, HER2-negative breast cancer. *Breast cancer*, *25*(4), 392-401. https://doi.org/10.1007/s12282-017-0812-x

20. Ruan, Y., Chen, L., Xie, D., Luo, T., Xu, Y., Ye, T., Wu, X. (2022). Mechanisms of cell adhesion molecules in endocrine-related cancers: a concise outlook. *Frontiers in endocrinology*, *13*, 865436. https://doi.org/10.3389/fendo.2022.865436

21. Desmedt, C., Pingitore, J., Rothé, F., Marchio, C., Clatot, F., Rouas, G., Sotiriou, C. (2019). ESR1 mutations in metastatic lobular breast cancer patients. *NPJ breast cancer*, *5*(1), 9. https://doi.org/10.1038/s41523-019-0104-z

22. Angelico, G., Broggi, G., Tinnirello, G., Puzzo, L., Vecchio, G. M., Salvatorelli, L., Caltabiano, R. (2023). Tumor infiltrating lymphocytes (TILS) and PD-L1 expression in breast cancer: a review of current evidence and prognostic implications from pathologist's perspective. *Cancers*, *15*(18), 4479. https://doi.org/10.3390/cancers15184479

23. Lotfinejad, P., Asghari Jafarabadi, M., Abdoli Shadbad, M., Kazemi, T., Pashazadeh, F., Sandoghchian Shotorbani, S., Baradaran, B. (2020). Prognostic role and clinical significance of tumor-infiltrating lymphocyte (TIL) and programmed death ligand 1 (PD-L1) expression in triple-negative breast cancer (TNBC): a systematic review and meta-analysis study. *Diagnostics*, *10*(9), 704. https://www.mdpi.com/2075-4418/10/9/704#

24. Bertucci, F., Gonçalves, A. (2017). Immunotherapy in breast cancer: the emerging role of PD-1 and PD-L1. *Current oncology reports*, *19*(10), 64. https://doi.org/10.1007/s11912-017-0627-0

25. Voutsadakis, I. A. (2020). High tumor mutation burden and other immunotherapy response predictors in breast cancers: associations and therapeutic opportunities. *Targeted oncology*, *15*(1), 127-138. https://doi.org/10.1007/s11523-019-00689-7

26. Casolino, R., Beer, P. A., Chakravarty, D., Davis, M. B., Malapelle, U., Mazzarella, L., Biankin, A. V. (2024). Interpreting and integrating genomic tests results in clinical cancer care: Overview and practical guidance. *CA: a cancer journal for clinicians*, *74*(3), 264-285. https://doi.org/10.3322/caac.21825

27. Satam, H., Joshi, K., Mangrolia, U., Waghoo, S., Zaidi, G., Rawool, S., Malonia, S. K. (2023). Next-generation sequencing technology: current trends and advancements. *Biology*, *12*(7), 997. https://www.mdpi.com/2079-7737/12/7/997#

28. Satam, H., Joshi, K., Mangrolia, U., Waghoo, S., Zaidi, G., Rawool, S., Malonia, S. K. (2024). Correction: Satam et al. Next-generation sequencing technology: Current trends and advancements. Biology 2023, 12, 997. *Biology*, *13*(5), 286. https://www.mdpi.com/2079-7737/13/5/286#

29. Cardoso, F., Paluch-Shimon, S., Schumacher-Wulf, E., Matos, L., Gelmon, K., Aapro, M. S., Bajpai, J., Barrios, C. H., Bergh, J., Bergsten-Nordström, E., Biganzoli, L., Cardoso, M. J., Carey, L. A., Chavez-MacGregor, M., Chidebe, R., Cortés, J., Curigliano, G., Dent, R. A., El Saghir, N. S., Winer, E. P. (2024). 6th and 7th International consensus guidelines for the management of advanced breast cancer (ABC guidelines 6 and 7). *The Breast*, *76*, 103756. https://doi.org/10.1016/j.breast.2024.103756

30. Kato, S., Kim, K. H., Lim, H. J., Boichard, A., Nikanjam, M., Weihe, E., Kurzrock, R. (2020). Real-world data from a molecular tumor board demonstrates improved outcomes with a precision N-of-One strategy. *Nature communications*, *11*(1), 4965. https://doi.org/10.1038/s41467-020-18613-3

31. Kopetz, S., Mills Shaw, K. R., Lee, J. J., Zhang, J., Litzenburger, B., Holla, V., Broaddus, R. R. (2019). Use of a targeted exome next-generation sequencing panel offers therapeutic opportunity and clinical benefit in a subset of patients with advanced cancers. *JCO Precision Oncology*, *3*, 1-14. https://doi.org/10.1200/PO.18.00213

32. Gibbs, S. N., Peneva, D., Cuyun Carter, G., Palomares, M. R., Thakkar, S., Hall, D. W., Yermilov, I. (2023). Comprehensive review on the clinical impact of next-generation sequencing tests for the management of advanced cancer. *JCO precision oncology*, *7*, e2200715. https://doi.org/10.1200/PO.22.00715

33. Godet, I., Gilkes, D. M. (2017). BRCA1 and BRCA2 mutations and treatment strategies for breast cancer. *Integrative cancer science and therapeutics*, *4*(1), 10-15761. https://doi.org/10.15761/ICST.1000228

34. Abdel-Razeq, H., Al-Omari, A., Zahran, F., Arun, B. (2018). Germline BRCA1/BRCA2 mutations among high risk breast cancer patients in Jordan. *BMC cancer*, *18*(1), 152. https://doi.org/10.1186/s12885-018-4079-1

35. Pederson, H. J., Narod, S. A. (2024). Commentary: Why is genetic testing underutilized worldwide? The case for hereditary breast cancer. *BJC reports*, *2*(1), 73. https://doi.org/10.1038/s44276-024-00099-x

36. Morgan, O., Belda, R., Schnur, J., Montgomery, G., Parmar, S., Chirivella, I., Cano, A. (2024). Prophylactic mastectomy and bilateral salpingo-oophorectomy in patients with breast cancer: a systematic review of postsurgical sexual function and menopausal hormone therapy symptom mitigation. *Sexual medicine reviews*, *12*(1), 3-13. https://doi.org/10.1093/sxmrev/qead020

37. Virga, A., Gianni, C., Palleschi, M., Angeli, D., Merloni, F., Maltoni, R., Bravaccini, S. (2024). A Novel AKT1, ERBB2, ESR1, KRAS, PIK3CA, and TP53 NGS assay: a non-invasive tool to monitor resistance mechanisms to hormonal therapy and CDK4/6 Inhibitors. *Biomedicines*, *12*(10), 2183. https://doi.org/10.3390/biomedicines12102183

38. Crucitta, S., Ruglioni, M., Lorenzini, G., Bargagna, I., Luculli, G. I., Albanese, I., Del Re, M. (2023). CDK4/6 inhibitors overcome endocrine ESR1 mutation-related resistance in metastatic breast cancer patients. *Cancers*, *15*(4), 1306. https://doi.org/10.3390/cancers15041306

Сүт безі қатерлі ісігінің молекулярлық-генетикалық профилі: BRCA мутацияларының рөлі, дербестендірілген емнің негізі ретінде герминальді және соматикалық альтерациялар

Самиғатова А.О. [1], Сәдуақасова А.Б. [2], Алтаева Н.З. [3], Жабағин Қ.Т. [4], Жақыпбекқызы Ж. [5], Сарсенғалиев Т.І. [6], Жабағина А.С. [7]

[1] PhD-студент, Астана медицина университеті, Астана, Қазақстан

[2] Ядролық медицина орталығының басшысы, Қазақстан Республикасы Президентінің Іс басқармасы Медициналық орталығы ауруханасы, Астана, Қазақстан

[3] Қауымдастырылған профессор, Медициналық генетика және молекулалық биология кафедрасының меңгерушісі, Астана медицина университеті, Астана, Қазақстан

[4] PhD, Ядролық медицина орталығының аға дәрігері, Қазақстан Республикасы Президентінің Іс басқармасы Медициналық орталығы ауруханасы, Астана, Қазақстан

[5] PhD-студент, Астана медицина университеті, Астана, Қазақстан

[6] Ядролық медицина орталығының радиоизотопты диагностика бөлімінің меңгерушісі, Қазақстан Республикасы Президентінің Іс басқармасы Медициналық орталығы ауруханасы, Астана, Қазақстан

[7] PhD, Радиолог дәрігер, Астана қаласының №3 емханасы, Астана, Қазақстан

Түйіндеме

Сүт безі қатерлі ісігі бүкіл әлемде әйелдер арасында ең таралған және әлеуметтік маңызды қатерлі ісіктердің бірі болып қала береді. Молекулярлық биология мен онкогенетикадағы жетістіктер сүт безі обырын диагностикалауға, болжауға және емдеуге деген көзқарастарды түбегейлі өзгертті, дербестендірілген медицинаға көбірек көңіл бөледі. Бұл шолу сүт безі қатерлі ісігінің молекулярлық-генетикалық ландшафтын зерттейді, герминальді және соматикалық мутациялар арасындағы айырмашылықтарға, олардың клиникалық маңыздылығына және жеке терапиялық стратегияларды басқарудағы рөліне назар аударады. Әдебиеттерді шолу нәтижелері герминальді мутациялары, әсіресе *BRCA1* және *BRCA2* - сүт безі обырының тұқым қуалайтын бейімділігімен тығыз байланысты екенін көрсетті, бұл тәуекелді бағалауға да, алдын алу стратегияларына да әсер етеді. Керісінше, соматикалық мутациялар, соның ішінде *TP53, PIK3CA* және *ESR1* өзгерістері ісіктің ерекшелігінде, емдеуге төзімділікте және аурудың өршуінде маңызды рөл атқарады. Сонымен қатар, толық геномды секвенирлеу арқылы анықталған герминальді және соматикалық мутация деректерін қамтитын интегративті молекулалық профильдеу дербестендірілген терапияда клиникалық шешім қабылдау үшін дәлірек негізді қамтамасыз етеді. Зерттеулер біріктірілген профильді емделушілер *PARP* тежегіштерін, эндокриндік терапияны және иммундық бақылау нүктесі ингибиторларын қоса, дәлірек терапевтік мақсатты тағайындаудан пайда көретінін көрсетті. Герминальді және соматикалық талдаулардың интеграциясы сүт безі қатерлі ісігімен ауыратын науқастарда терапевтік нәтижелер мен болжамды жақсартатын нақтыланған медицинаны жүзеге асырудағы маңызды қадам болып табылады.

Түйін сөздер: сүт безі қатерлі ісігі, BRCA1/2, герминальді соматикалық мутация, толық геномды секвенирлеу, нақтыланған медицина.

Молекулярно-генетический профиль рака молочной железы: Роль мутаций *BRCA*, герминальные и соматические альтерации как основа персонализированной терапии

Самиғатова А.О. [1], Сәдуақасова А.Б. [2], Алтаева Н.З. [3], Жабағин Қ.Т. [4], Жақыпбекқызы Ж. [5], Сарсенғалиев Т.І. [6], Жабағина А.С. [7]

[1] PhD-студент, Медицинский университет Астана, Астана, Казахстан

[2] Руководитель Центра ядерной медицины, Больница Медицинского центра Управления делами Президента Республики Казахстан, Астана, Казахстан

[3] Ассоциированный профессор, Заведующая кафедры медицинской генетики и молекулярной биологии, Медицинский университет Астана, Астана, Казахстан

[4] PhD, Старший врач Центра ядерной медицины, Больница Медицинского центра Управления делами Президента Республики Казахстан, Астана, Казахстан

[5] PhD-студент, Медицинский университет Астана, Астана, Казахстан

[6] Заведующий отделением радиоизотопной диагностики центра ядерной медицины, Больница Медицинского центра Управления делами Президента Республики Казахстан, Астана, Казахстан

[7] PhD, Врач радиолог, Поликлиника №3 города Астаны, Астана, Казахстан

Резюме

Рак молочной железы остается одним из самых распространенных и социально значимых злокачественных заболеваний среди женщин во всем мире. Достижения молекулярной биологии и онкогенетики существенно изменили подходы к диагностике, прогнозированию и лечению рака молочной

железы, при этом все большее внимание уделяется персонализированной медицине. В данном обзоре рассматривается молекулярно-генетический ландшафт рака молочной железы с акцентом на различия между герминальными и соматическими мутациями, их клиническое значение и роль в определении индивидуальных терапевтических стратегий. Результаты обзора литературы показали, что герминальные мутации, особенно в генах *BRCA1* и *BRCA2*, тесно связаны с наследственной предрасположенностью к раку молочной железы, влияя как на оценку риска, так и на профилактические стратегии. Напротив, соматические мутации, включая изменения в генах *TP53*, *PIK3CA* и *ESR1*, играют ключевую роль в поведении опухоли, резистентности к лечению и прогрессировании заболевания. Более того, интегративное молекулярное профилирование с использованием секвенирования нового поколения, включающее данные как о герминальных, так и о соматических мутациях, обеспечивает более точную основу для принятия клинических решений при персонализированной терапии. Исследования показали, что пациенты с комбинированным профилированием получают преимущества от более точного терапевтического воздействия, включая ингибиторы *PARP*, эндокринную терапию и ингибиторы иммунных контрольных точек. Интеграция герминального и соматического анализа представляет собой критически важный шаг на пути к реализации прецизионной медицины, в конечном итоге улучшая результаты лечения и прогноз у пациентов с раком молочной железы.

Ключевые слова: рак молочной железы, *BRCA1/2*, герминальная соматическая мутация, секвенирование нового поколения, прецизионная медицина.