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The Importance of Genetic Testing in Patients with Breast Cancer for Identifying Risk Groups, Selecting Treatment and Prevention Strategies, and Determining Prognosis

Introduction. Breast cancer (BC) is one of the most common malignancies worldwide and remains a significant public health challenge [33]. Global cancer statistics indicate that 2.3 million new cases of BC were diagnosed in 2020, representing nearly 12.0 % of all new cancer diagnoses and causing 685,000 deaths that year [36]. As of January 1, 2025, there were approximately 18.6 million people in the United States with a history of cancer, and this number is projected to exceed 22.0 million by 2035 [38].

Although the majority of BC cases are sporadic, a substantial proportion is associated with inherited genetic predisposition [38]. Mutations in certain genes account for approximately 5.0-10.0 % of all breast cancer cases [23].

Studies have shown that breast cancer 1 (BRCA1) and BRCA2 genes are recognized as crucial tumor suppressors that play a vital role in regulating cell growth and repairing deoxyribonucleic acid (DNA) [34]. When mutated, their dysfunction significantly increases the risk of developing several cancers, including breast cancer [14].

In addition to BRCA1 and BRCA2, many other genes are consistently listed in numerous sources [2, 4, 23, 38].

The effectiveness of poly(ADP-ribose) polymerase inhibitors (PARP), human epidermal growth factor receptor 2 (HER2) inhibitors, and other targeted therapies in the treatment of hereditary breast cancer makes it possible to detect hereditary mutations of the BRCA1/2 genes, etc., and effectively personalize treatment and prevention strategies [1, 2, 4, 23, 28, 34, 38].

This evidence justifies the feasibility of conducting an analysis to evaluate the role of genetic testing in patients with breast cancer for identifying risk groups, choosing tactics and strategies for treatment, prevention and prognosis.

The aim of the study. To assess the significance of genetic testing in patients with breast cancer, based on the analysis of published research results, in order to optimize treatment and prevention strategies.

Materials and methods. A literature search and analysis were performed in the PubMed/MEDLINE, Scopus, and Web of Science databases using the keywords: breast cancer, genetic testing, treatment, prevention. Included materials comprised original articles, systematic reviews, meta-analyses, and guidelines of international medical societies, along with national guidelines published before August 1, 2025. Only articles in English or Ukrainian were considered. Low-quality studies were excluded using standard criteria, including small sample size, case reports, or lack of statistically significant findings compared with controls or placebo [4]. Narrative reviews, case series, pediatric studies, and cohort studies with <100 participants were excluded.

To perform this study, the results of 3 randomized clinical trials, 27 prospective clinical studies, 7 literature reviews and meta-analyses, 4 international society guidelines, and 1 national guideline were selected and analyzed, which are referenced in the list of references.

Results and discussion. The analysis of publications shows that genes, depending on the risk of predisposition to hereditary breast cancer, are divided into genes of high and moderate penetrance.

High-Penetrance Genes include [2, 4, 23, 38]:

BRCA1 and BRCA2, which are the most significant contributors to hereditary BC, are responsible for more than 50.0 % of pathogenic germline variants found in families with hereditary breast cancer [1, 2, 4, 23, 38]. They function as critical tumor suppressor genes involved in DNA repair, especially homologous recombination. Mutations in BRCA1 and BRCA2 lead to a significant

increase in the lifetime risk of breast cancer (more than 60.0 % for BRCA1 and more than 60.0 % for BRCA2 by the age of 80), as well as an increased risk of ovarian, prostate and pancreatic cancer [15]. These tumors respond well to PARP inhibitors [14].

PALB2 (Partner and localizer of BRCA2) is a high-risk gene interacting with BRCA2 and playing a major role in DNA repair [1, 2, 4, 23, 38]. Pathogenic variants in PALB2 confer a 40-60 % lifetime BC risk [1, 4].

TP53 ("tumor protein p53") is a key tumor suppressor gene essential for cell cycle regulation, DNA repair, and apoptosis. TP53 is classified as a high-risk gene for breast cancer, with a lifetime risk of 40.0 % [15]. It demonstrates sensitivity to PARP inhibitors [28].

PTEN ("phosphatase and tensin homolog") as a tumor suppressor gene, PTEN is responsible for regulating cell proliferation, preventing their uncontrolled growth and division [6]. Mutations in PTEN indicate a high risk of breast cancer [4, 6].

CDH1 ("cadherin 1"): Germline pathogenic variants in CDH1 are associated with hereditary diffuse gastric cancer (HDGC) syndrome, as well as with a high risk of lobular breast cancer (39.0-55.0 % in women under 80 years of age) [4].

STK11 ("serine / threonine kinase 11") also known as LKB1, encodes a serine / threonine kinase that functions as a tumor suppressor, regulates cell polarity and energy metabolism [14]. Inherited mutations in STK11 provoke Peutz - Jeghers syndrome (Jan Peutz - Harold Jeghers), an autosomal dominant condition characterized by the growth of polyps in the gastrointestinal tract, pigmented spots on the skin and mucous membranes of the mouth, and an increased susceptibility to a number of epithelial cancers, including BC [14]. It is considered to be a high BC risk gene [4, 14].

Moderate-Penetrance Genes:

CHEK2 (checkpoint kinase 2) is a tumor suppressor gene that plays a critical role in DNA damage signaling pathways, directly phosphorylating and regulating key proteins such as p53 and BRCA1 [4, 14]. Specific mutations, such as CHEK21100delC, are associated with a twofold increase in the risk of breast cancer in women and a tenfold increase in men [4, 14, 23]. CHEK2 is classified as a moderate-risk gene, with a lifetime risk of breast cancer of 25.0-30.0 % [4].

ATM (Ataxia-telangiectasia mutated) is central to the body's response to DNA damage, encoding a protein that helps detect double-stranded DNA breaks and activates repair [4, 14, 23]. Mutations in ATM compromise the cell's ability to correct genetic errors, leading to genomic instability and increased risk for several types of cancer, particularly breast cancer. Early magnetic resonance imaging (MRI) and mammography (from age 30-35) are recommended [4, 14, 23].

BARD1 (BRCA1-associated RING Domain 1) encodes a protein that interacts with BRCA1, functioning together to repair damaged DNA and inhibit the oncogenic process [30]. Mutations in BARD1 may disrupt this function, leading to an increased risk of breast cancer, although the exact magnitude of this risk is less well defined compared with BRCA1/2. [30]. It has sensitivity to PARP inhibitors [30].

BRIP1 (BRCA1-interacting protein 1) is a tumor suppressor gene that encodes a helicase that plays a vital role in homologous recombination DNA repair through its interaction with BRCA1 [18]. Mutations in BRIP1 are significantly associated with the onset of breast cancer. Overexpression of BRIP1 has also been correlated with worse disease-specific, metastasis-free, recurrence-free, and overall survival in breast cancer patients [15, 18].

RAD51C and RAD51D. These genes belong to the RAD51-associated protein family, which are crucial for the repair of double-strand DNA breaks by homologous recombination [32]. Pathological mutations in both RAD51C and RAD51D confer susceptibility to both breast cancer and ovarian cancer [32]. Women with RAD51D mutations have an increased lifetime risk of breast cancer (approximately 19.0 % by age 80.0), and these breast cancers are often triple-negative [15, 32].

Hereditary breast cancer often arises not from isolated gene defects but from disruptions in a complex, interconnected network of DNA damage response and repair pathways. This highlights a systemic vulnerability to genomic instability. For example, PALB2 is a partner of BRCA2 [2], BARD1 interacts with BRCA1 [30], and BRIP1 interacts with BRCA1 [18]. In addition, ATM phosphorylates CHK2, which in turn regulates p53 and BRCA1 [4]. This complex network means that a pathogenic variant in one gene can have cascading effects on the entire DNA damage response system, leading to genomic instability.

Fundamental understanding is crucial for the development of personalized treatments that exploit these pathway deficiencies. The clinical utility of genetic testing extends beyond simply identifying "at-risk groups" to more precise risk stratification across the spectrum of penetrance.

While highly penetrant genes require aggressive risk reduction strategies (e.g., prophylactic surgery), moderately penetrant genes confer a lower but still significantly increased risk (e.g., two-fold for CHEK2, 25.0-30.0 % lifetime risk for CHEK2/ATM, 19.0 % for RAD51D) [4].

The appearance of Next Generation Sequencing (NGS) technologies has marked a revolutionary breakthrough, enabling high-throughput multigene analysis and even whole exome sequencing (WES) or whole genome sequencing (WGS) [40]. NGS provides a powerful and efficient tool for uncovering the complex genetic basis of multigenic diseases such as cancer, generating vast amounts of data suitable for in-depth analysis [40]. More comprehensive NGS approaches, such as whole-exome sequencing (WES) and whole-genome sequencing (WGS), offer a broader exploration of the genomic landscape. WES sequences nearly all protein-coding regions of DNA, whereas WGS sequences the entire genome, including both coding and non-coding regions [40]. Although these methods are more expensive and generate significantly larger sets of information, they are invaluable for disco-

vering new susceptibility genes and for cases where initial panel testing is uninformative [40].

Targeted gene sequencing, or "NGS gene panels", is considered the most accessible and widely used approach [40]. These panels enable targeted analysis of a selected set of genes or specific regions that are already known or highly suspected to be involved in the pathogenesis of certain diseases [40]. They have significant advantages in terms of high-throughput analysis, cost-effectiveness, and rapid turnaround time, making them ideal for use in the clinic [40]. Examples of such panels include the Rapid Hereditary Breast Cancer Treatment Decision Panel, designed for urgent treatment decisions; the Hereditary Breast/Gynecologic Cancer Panel, and others, each tailored to specific cancer syndromes and gene sets [4, 40].

NGS tests can identify both germline (inherited, such as BRCA1/2) and somatic mutations acquired during a person's lifetime [12]. Somatic NGS is particularly recommended for patients with metastatic or unresectable breast cancer, as it can identify specific mutations that may be targeted for treatment [12]. Leading professional organizations, including the National Comprehensive Cancer Network, the American Society of Clinical Oncology, the Society of Surgical Oncology, and the European Society for Medical Oncology [1, 4], regularly issue and update guidelines to standardize and optimize the practice of genetic testing for hereditary susceptibility to breast cancer [4]. The recommendations of these societies, as well as the Ukrainian guideline updated in 2025, are evidence-based, constantly updated with new scientific information, and are crucial for formulating clinical decisions [4] for both risk management and treatment. The development of targeted therapies, in particular PARP inhibitors, has been a significant catalyst for expanding the basis for genetic testing.

According to the main provisions of these guidelines, the main reasons for offering BRCA1/2 genetic testing are as follows:

- Newly diagnosed breast cancer (stage I-III or IV/metastatic) ≤65 years [1, 4, 23].
- Newly diagnosed breast cancer (stage I-III or IV/metastatic) >65 years (PARP inhibitor candidates or triple-negative breast cancer or personal/family history suggesting a pathogenic variant or male gender or Ashkenazi Jewish ancestry/founding mutations) [4].
- Recurrent breast cancer (local or metastatic) - PARP inhibitor candidates [4].
- Second primary breast cancer (contralateral or ipsilateral) [4].
- Personal history of breast cancer (without active disease) ≤ 65 years [4].
- Healthy person with family history of cancer - testing for BRCA1/2, PALB2, other genes based on clinical/family history [4, 23].

Interpretation of genetic testing results. A positive genetic test result and the detection of BRCA1 gene mutations provide patients with crucial information about their increased risk of contralateral breast cancer and ovarian cancer and an informed decision about risk-reducing interventions [4, 23].

A negative genetic test result means that no known pathogenic mutations have been detected in the tested genes [4]. However, the informativeness of a negative result depends on the clinical context. It is only fully informative if a known pathogenic mutation has already been identified in a close family member [4]. In the absence of such a known familial mutation, a negative result should be interpreted with caution, especially in people with a strong personal or family history of cancer, as it does not necessarily rule out an increased risk. This is because other untested genes or as yet undiscovered genetic factors may still be contributing to their predisposition [16].

Variants of uncertain (or unknown) significance (VUS) are genetic alterations whose clinical significance, pathogenicity or benignity, is currently unknown [16]. In particular, VUS are detected in a significant proportion of BRCA sequencing results, approximately 10.0-20.0 % [16].

The results of genetic testing are not interpreted in isolation, but are integrated with age, comprehensive family history, personal medical history, and other risk factors to help formulate an individualized treatment plan [23].

For patients with pathogenic variants, the directly obtained information influences local treatment decisions, such as the extent of surgical treatment (e.g., mastectomy), and the prescription of systemic treatment, in particular the use of PARP inhibitors [2, 4]. In addition, genetic testing results inform the need for enhanced surveillance protocols; for example, carriers of ATM mutations are usually recommended to start MRI screening and mammography as early as possible, often at the age of 30-35 [4]. For specific genes such as CDH1, in addition to the risk of breast cancer, genetic testing results require individual follow-up for other associated cancers, such as esophagogastroduodenoscopy with targeted biopsy of the gastric mucosa for screening diagnosis of gastric cancer [4].

Genetic testing can predict the effectiveness of breast cancer treatment and generally determine the prognosis of the disease. Testing more genes may provide more information about the effectiveness of treatment and prognosis of breast cancer [4].

The Trial Assigning Individualized Options for Treatment (TAILORx) is one of the largest clinical trials to examine the effectiveness of the Oncotype DX test. Oncotype DX is a 21-gene test for breast cancer patients that helps predict the benefit of chemotherapy in early-stage, hormone-responsive (HR+), HER2-negative breast cancer with up to 3 lymph nodes involved. The TAILORx trial showed that patients with low to intermediate risk of BC recurrence, as assessed by the Recurrence Score (0 to 25), do not benefit from chemotherapy and can safely receive hormone therapy alone [13].

A study by M. Potrony et al. also showed that the Recurrence Score can predict chemotherapy benefit in patients with breast cancer [28].

K. Kalinsky et al. [17] analyzed the results of Oncotype DX testing and chemotherapy efficacy from 2019 to 2020 in 173 patients, most of whom were HR+, HER2- and had up to 3 affected lymph nodes. Long-term results between the Oncotype DX groups over 20 years did not reveal a significant difference in disease recurrence or mortality, indicating that the Oncotype DX test results accurately predict overall chemotherapy benefit [17].

OncotypeDX testing is recommended in the following cases [4, 23]:

patient age ≤ 65 years and:

- T1c N0 tumors of stage II-III;
- T2 N0 tumors of any stage;
- T1-T2 N1 tumors of any stage;
- T3 N0/N1 tumors of any stage.

The European Society for Medical Oncology (ESMO) recommends Oncotype DX testing as a tool for assessing the risk of BC recurrence [21].

In addition to Oncotype DX, there are other tests that analyze genes to predict tumor recurrence and treatment options:

The MammaPrint test analyzes 70 genes and categorizes the risk of recurrence as "low" or "high". It may be useful in cases where the cancer has spread to the lymph nodes [3, 27].

Breast Cancer Prognostic Gene Signature Assay (Prosigna) - Prosigna tests 50 genes and helps determine the molecular subtype of breast cancer. It may provide additional prognostic information, especially for postmenopausal women [19]. However, it is believed [19, 31] that the Prosigna assay can only be used for breast cancer diagnosed in postmenopausal women that is stage I or II and has no lymph nodes involved, or stage II with one to three lymph nodes involved, or has hormone receptor-positive disease, or is invasive, or has been treated with surgery and hormonal drugs. It has also been proposed to use the Breast Cancer Index (BCI), which is based on gene expression and consists of two functional biomarker panels: the ratio of HOXB13 mutations, which are associated with an increased risk of prostate cancer in men, to interleukin IL17BR (H/I), and the Molecular Grade Index (MGI), which examines important estrogen signaling and proliferative pathways in the presence of breast cancer [24, 42]. The MRI Prognostic Score is an algorithmic combination of the H/I ratio and MGI and reports the individualized risk of overall and late distant recurrence [10, 24, 42].

These comprehensive genetic tests can provide more information about genetic mutations than testing for BRCA1 or BRCA2 alone, but these tests are still limited by their high cost and the small number of laboratories.

Given that genetic mutations are a significant, but not the only, risk factor for oncopathological lesions, special questionnaires have been created that cover various risk factors for oncological diseases. In particular, the Breast Cancer Risk Assessment Tool (BCRAT) questionnaire allows you to estimate the risk of developing invasive breast cancer in a woman over the next five years and up to the age of 90 [29]. The online BCRAT calculator [29] includes questions about the site of the breast lesion, the presence of metastases in regional lymph nodes, previous chest radiotherapy, the presence of a mutation in the BRCA1 or BRCA2 gene, or the diagnosis of a genetic syndrome that may be associated with an increased risk of breast cancer. The patient's age, race/ethnicity, or place of birth are also taken into account. Information is collected on the woman's age at first menstruation, date of birth of her first child, and first-degree relatives (mother, sisters, daughters) who have had breast cancer [29]. BCRAT is also used to predict the effectiveness of breast cancer treatment, assessing it at baseline and after 2.5 and 5 years of adjuvant endocrine therapy [29].

Tactics and strategy for the treatment and prevention of breast cancer taking into account the results of genetic testing.

Targeted individualized therapy is aimed at repairing DNA in patients with gene mutations, which increases the effectiveness of complex adjuvant treatment of cancer [5, 7, 10, 20, 26, 29, 35, 37, 39, 41].

PARP inhibitors: Olaparib (Lynparza), which is the cornerstone of targeted individualized therapy for breast cancer with specific genetic mutations [41]. It is especially effective for the treatment of tumors containing pathogenic variants in BRCA1, BRCA2 and PALB2, since these genes play a crucial role in DNA repair pathways [10]. Olaparib has been approved by the US Food and Drug Administration (FDA) for adjuvant treatment after chemotherapy for patients with high-risk, early-stage breast cancer and inherited BRCA1 or BRCA2 mutations [10, 41]. It is also used in the presence of metastases for patients with BRCA1/2 mutations [20].

Other targeted therapies. NGS tests can detect somatic mutations in genes such as AKT1, ESR1, and PIK3CA in the presence of metastatic breast cancer for which specific targeted therapies are available [5]. For example, PIK3CA mutations in ER/PR-positive breast cancer can be targeted with Alpelisib (Piqray) [5].

HER2-targeted therapy, including trastuzumab (Herceptin), pertuzumab (Perjeta), tukatinib (Tukysa), and trastuzumab deruxtecan (Enhertu), is a recommended treatment for HER2-positive or HER2-low breast cancer [25, 29, 35, 37, 39].

CDK4/6 inhibitors, such as palbociclib (Ibrance), ribociclib (Kisqali), and abemaciclib (Verzenio), are commonly used for patients with estrogen receptor (ER) and progesterone receptor (PR)-positive, i.e., ER/PR-positive advanced breast cancer [7].

Immunotherapy: Immune checkpoint inhibitors, such as pembrolizumab (Keytruda), are approved for triple-negative breast cancer that is metastatic or locally recurrent and inoperable, especially if it is positive for the ligand for the PD-L1 receptor, which is expressed on the surface of tumor cells. [26] Pembrolizumab is also approved for the treatment of patients with early-stage triple-negative breast cancer at high risk of recurrence, used in combination with chemotherapy as neoadjuvant therapy before surgery and alone after surgery [26].

Preventive surgery

Bilateral reduction mastectomy. This surgical procedure involves the removal of both breasts and is a highly effective preventive measure [9, 15]. It has been shown to reduce the risk of breast cancer by at least 95.0 % in women who carry pathogenic variants of BRCA1 or BRCA2, and by up to 90.0 % in women with a strong family history of breast cancer [9]. Although mastectomy provides a significant risk reduction, it is a major operation with potential complications and significant emotional and psychological impact, including changes in body image, chronic pain, and loss of sensation [22].

Bilateral prophylactic salpingo-ophorectomy (BSO) involves the surgical removal of both ovaries and fallopian tubes. Its primary goal is to significantly reduce the risk of ovarian and fallopian tube cancer in BRCA1/2 carriers [8]. BSO may also help reduce the risk of breast cancer, especially for BRCA1 carriers, and it improves long-term outcomes for patients with BRCA variants [8]. An important consequence of BSO is the induction of early menopause [8].

Enhanced surveillance protocols. For individuals with pathogenic variants, enhanced and early surveillance is a crucial component of risk management. This typically includes more frequent and expanded breast examinations, such as mammography and breast MRI [4]. For example, patients with ATM mutations are advised to begin screening with MRI and mammography earlier, often at the age of 30-35 years [4]. In addition to breast-specific surveillance, specific protocols for associated cancers, such as annual esophagogastroduodenoscopy with targeted gastric mucosal biopsy, are recommended for genes such as CDH1 [4].

Chemoprophylaxis. In some cases, pharmacological interventions known as chemoprophylaxis (drugs aimed at reducing the risk of cancer) may be considered for individuals with specific genetic mutations, such as BARD1 mutations, depending on their overall individual risk profile [35].

Conclusions. Genetic testing in women with breast cancer or a strong family history enables identification of risk groups, optimization of treatment strategies, and appropriate selection of preventive measures. The use of PARP, HER2, and other inhibitors in the case of detection of inherited gene mutations in the adjuvant treatment of breast cancer helps to effectively personalize treatment and prevention strategies, improve the prognosis, quality, and length of life of patients.

References

1. Рак молочної залози на ранніх стадіях: клінічна настанова, заснована на доказах. Наказ МОЗ України № 195 від 03.02.2025 р. (Early breast cancer: An evidence-based clinical setting. Order of the Ministry of Health of Ukraine No. 195 dated 2025 Feb 03).
2. Abdel-Razeq H. Surgical options for patients with early-stage breast cancer and pathogenic germline variants: An oncologist perspectives. Frontiers in Oncology. 2023;13:1265197. doi:10.3389/fonc.2023.1265197
3. Andre F, Ismaila N, Allison KH et al. Biomarkers for adjuvant endocrine and chemotherapy in early-stage breast cancer: ASCO guideline update. J Clin Oncol. 2022;40(16):1816-1837. doi:10.1200/JCO.22.00067
4. Bedrosian I, Somerfield MR, Achatz MI, Boughey JC, Curiglian G, Friedman S et al. Germline testing in patients with breast cancer: asco-society of surgical oncology guideline. J Clin Oncol. 2024;42:584-604. doi:10.1200/JCO.23.02225
5. Bello Roufai D, Gonçalves A, De La Motte Rouge T, Akla S, Blonz C, Grenier J et al. Alpelisib and fulvestrant in PIK-3CA-mutated hormone receptor-positive HER2-negative advanced breast cancer included in the French early access program. Oncogene. 2023;42(23):1951-1956. doi:10.1038/s41388-022-02585-3
6. Bergholz JS, Wang Q, Wang Q, Ramseier M, Prakadan S, Wang W et al. PI3Kβ controls immune evasion in PTEN-deficient breast tumours. Nature. 2023;617(7959):139-146. doi:10.1038/s41586-023-05940-w
7. Braal CL, Jongbloed EM, Wilting SM, Mathijssen RHJ, Koolen SLW, Jager A. Inhibiting CDK4/6 in breast cancer with Palbociclib, Ribociclib, and Abemaciclib: Similarities and Differences. Drugs. 2021;81(3):317-331. doi:10.1007/s40265-020-01461-2
8. Conduit C, Milne RL, Friedlander ML, Phillips KA. Bilateral salpingo-oophorectomy and breast cancer risk for BRCA1 and BRCA2 mutation carriers: Assessing the evidence. Cancer Prev Res (Phila). 2021;14(11):983-994. doi:10.1158/1940-6207.CAPR-21-0141
9. Corso G, Magnoni F, Veronesi P. Points to consider regarding de-escalation surgery in high-risk breast cancer. Ann Surg Oncol. 2022;29(13):8084-8089. doi:10.1245/s10434-022-12542-9
10. Daly GR, AlRawashdeh MM, McGrath J, Dowling GP, Cox L, Naidoo S et al. PARP inhibitors in breast cancer: A short communication. Currt Oncol Rep. 2024;26(2):103-113. doi:10.1007/s11912-023-01488-0
11. Dhungana A, Vannier A, Zhao F, Freeman JQ, Saha P, Sullivan M et al. Development and validation of a clinical breast cancer tool for accurate prediction of recurrence. NPJ Breast Cancer. 2024;10(1);46. doi:10.1038/s41523-024-00651-5
12. Freitas AJAd, Causin RL, Varuzza MB, Calfa S, Hidalgo Filho CMT, Komoto TT et al. Liquid biopsy as a tool for the diagnosis, treatment, and monitoring of breast cancer. Int J Mol Sci. 2022;23(17):9952. doi:10.3390/ijms23179952
13. Giorgi Rossi P, Lebeau A, Canelo-Aybar C, Saz-Parkinson Z, Quinn C, Langendam M et al. Recommendations from the European Commission Initiative on Breast Cancer for multigene testing to guide the use of adjuvant chemotherapy in patients with early breast cancer, hormone receptor positive, HER-2 negative. Br J Cancer. 2021;124(9):1503-1512. doi:10.1038/s41416-020-01247-z
14. Huber-Keener KJ. Cancer genetics and breast cancer. Best Pract Res Clini Obstet Gynaecol. 2022;82:3-11. doi:10.1016/j.bpobgyn.2022.01.007
15. Irelli A, Patruno LV, Chiatamone Ranieri S, Di Giacomo D, Malatesta S, Alesse E et al. Role of breast cancer risk estimation models to identify women eligible for genetic testing and risk-reducing surgery. Biomedicines. 2024;12(4);714. doi: 10.3390/biomedicines12040714

16. Jimenez-Sainz J, Jensen RB. Imprecise medicine: BRCA2 Variants of uncertain significance (VUS), the challenges and benefits to integrate a functional assay workflow with clinical decision rules. Genes. 2021;12(5):780. doi:10.3390/genes12050780
17. Kalinsky K, Barlow WE, Gralow JR, Meric-Bernstam F, Albain KS, Hayes DF et al. (2021). 21-Gene assay to inform chemotherapy benefit in node-positive breast cancer. N Eng J Med. 2021;385(25):2336-2347. doi:10.1056/NEJMoa2108873
18. Khan U, Khan MS. Prognostic value estimation of BRIP1 in breast cancer by exploiting transcriptomics data through bioinformatics approaches. Bioinform Biol Insights. 2021;15:11779322211055892. doi:10.1177/11779322211055892
19. Kjällquist U, Acs B, Margolin S, Karlsson E, Kessler LE, Garcia Hernandez S et al. Real world evaluation of the prosigna/PAM50 test in a node-negative postmenopausal Swedish population: A multicenter study. Cancers (Basel). 2022;14(11):2615. doi:10.3390/cancers14112615
20. Lee A, Moon BI, Kim TH. BRCA1/BRCA2 pathogenic variant breast cancer: Treatment and prevention strategies. Ann Lab Med. 2020;40(2):114-121. doi:10.3343/alm.2020.40.2.114
21. Loibl S, André F, Bachelot T, Barrios CH, Bergh J, Burstein HJ et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2024;35(2):159-182. doi:10.1016/j.annonc.2023.11.016
22. Murugappan A, Khanna A. Interventional treatment options for post-mastectomy pain. Curr Oncol Rep. 2023;25(10):1175-1179. doi:10.1007/s11912-023-01435-z
23. Nagy P, Papp J, Grolmusz VK, Bozsik A, Pócza T, Oláh E et al. Comprehensive clinical genetics, molecular and pathological evaluation efficiently assist diagnostics and therapy selection in breast cancer patients with hereditary genetic background. Int J Mol Sci. 2024;25(23):12546. doi:10.3390/ijms252312546
24. Noordhoek I, Treuner K, Putter H, Zhang Y, Wong J, Meershoek-Klein Kranenbarg E et al. Breast cancer index predicts extended endocrine benefit to individualize selection of patients with HR+early-stage breast cancer for 10 years of endocrine therapy. Clin Cancer Res. 2021;27(1):311-319. doi:10.1158/1078-0432.CCR-20-2737
25. Novillo A, Gaibar M, Romero-Lorca A, Malón D, Antón B, Moreno A et al. HER2 and BARD1 polymorphisms in early HER2-positive breast cancer patients: Relationship with response to neoadjuvant anti-HER2 treatment. Cancers (Basel). 2023;15(3):763. doi:10.3390/cancers15030763
26. Pembrolizumab (Keytruda): CADTH Reimbursement Review: Therapeutic area: Triple-negative breast cancer [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2023 Mar. Report No.: PC0295CL.
27. Piccart M, van 't Veer LJ, Poncet C, Lopes Cardozo JMN, Delaloge S, Pierga J-Y et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. Lancet Oncol. 2021;22(4):476-488. doi:10.1016/S1470-2045(21)00075-8
28. Potrony M, Morales-Romero B, Moreno L, Pastor B, Grau E, Badenas C et al. Considerations for hereditary breast and ovarian cancer syndrome molecular diagnosis: experience from the clinical practice. Breast Cancer Res Treat. 2025;210(3):507-519. doi:10.1007/s10549-025-07643-4
29. Randall M, Akers R, Rao R. A review of current and future antibody drug conjugates in breast cancer. Curr Treat Options Oncol. 2024;25(12):1506-1516. doi:10.1007/s11864-024-01276-3
30. Rofes P, Del Valle J, Torres-Esquius S, Feliubadaló L, Stradella A, Moreno-Cabrera JM et al. BARD1 pathogenic variants are associated with triple-negative breast cancer in a Spanish hereditary breast and ovarian cancer cohort. Genes (Basel). 2021;12(2):150. doi:10.3390/genes12020150
31. Sanft TB, Wong J, O'Neal B, Siuliukina N, Jankowitz RC, Pegram MD et al. Impact of the breast cancer index for extended endocrine decision-making: First results of the prospective BCI registry study. J Nat Compre Canc Netw. 2024;22(2):99-107. doi:10.6004/jnccn.2023.7087
32. Shi Y, Shen M, Xu, M, Tao M, Chen K, Zhu Q. Comprehensive analysis of the expression and prognosis for RAD51 family in human breast cancer. Int J Gen Med. 2022;15:4925-4936. doi:10.2147/IJGM.S350971
33. Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. CA: Cancer J Clin. 2025;75(1):10-45. doi:10.3322/caac.21871
34. Subaşıoğlu A, Güç ZG, Gür EÖ, Tekindal MA, Atahan MK. Genetic, surgical and oncological approach to Breast cancer, with BRCA1, BRCA2, CDH1, PALB2, PTEN and TP53 variants. Eur J Breast Health. 2023;19(1):55-69. doi:10.4274/ejbh.galenos.2022.2022-7-2
35. Sun L, Jia X, Wang K, Li M. Unveiling the future of breast cancer therapy: Cutting-edge antibody-drug conjugate strategies and clinical outcomes. Breast. 2024;78:103830. doi:10.1016/j.breast.2024.103830
36. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: Cancer J Clin. 2021;71(3):209-249. doi: 10.3322/caac.21660
37. von Arx C, De Placido P, Caltavituro A, Di Rienzo R, Buonaiuto R, De Laurentiis M et al. The evolving therapeutic landscape of trastuzumab-drug conjugates: Future perspectives beyond HER2-positive breast cancer. Cancer Treat Rev. 2023;113:102500. doi:10.1016/j.ctrv.2022.102500
38. Wagle NS, Nogueira L, Devasia TP, Mariotto AB, Yabroff KR, Islami F et al. Cancer treatment and survivorship statistics, 2025. CA: Cancer J Clin. 2025;75(4):308-340. doi:10.3322/caac.70011
39. Yoon J, Oh DY. HER2-targeted therapies beyond breast cancer - an update. Nat Rev Clin Oncol. 2024;21(9):675-700. doi:10.1038/s41571-024-00924-9
40. Zelli V, Compagnoni C, Cannita K, Capelli R, Capalbo C, Di Vito Nolfi et al. Applications of next generation sequencing to the analysis of familial breast/ovarian cancer. High Throughput. 2020;9(1):1. doi:10.3390/ht9010001
41. Zeng Y, Arisa O, Peer CJ, Fojo A, Figg,WD. PARP inhibitors: A review of the pharmacology, pharmacokinetics, and pharmacogenetics. Semin Oncol. 2024;51(1-2):19-24. doi:10.1053/j.seminoncol.2023.09.005
42. Zooravar D, Radkhah H, Amiri BS, Soltani P. Association between triglyceride-glucose index and breast cancer: A systematic review and meta-analysis. Cancer Rep (Hoboken). 2025;8(4):e70194. doi:10.1002/cnr2.70194

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Conflict of interests

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The Importance of Genetic Testing in Patients with Breast Cancer for Identifying Risk Groups, Selecting Treatment and Prevention Strategies, and Determining Prognosis

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Introduction. Breast cancer (BC) remains one of the most common malignant neoplasms worldwide. Mutations in certain genes are the cause of 5.0-10.0 % of all cases of BC, therefore, timely genetic diagnostics can allow for effective prevention, the selection of targeted therapy, and the assessment of the prognosis of the disease.

The aim of the study . Determination of the significance of genetic testing in patients with breast cancer based on the analysis of published research results for choosing their treatment and prevention strategies.

Materials and methods. The search and analysis for literary sources was carried out among publications in open databases PubMed/MEDLINE, SCOPUS, WEB of SCIENCE and related to the keywords: breast cancer, genetic research, treatment, prevention.

Results. The study highlights the shift from focusing on BRCA1/2 genes to the use of comprehensive multigene panels, as well as the role of genetic diagnostics in selecting personalized treatment and prevention strategies for breast cancer. The interpretation of genetic study results is emphasized, with a focus on the use of tests such as Oncotype DX, MammaPrint, Prosigna, and others, which help predict the benefit of chemotherapy and assess the risk of breast cancer recurrence. The article briefly reviews the latest diagnostic technologies, such as multigene panels and liquid biopsy. Examples of targeted therapies based on BRCA1/2 and other gene mutations are described.

Conclusions. Genetic testing in women with breast cancer or with a heavy family history allows to identify risk groups, determining the tactics and strategy of adjuvant treatment, and choosing preventive measures. The use of PARP, HER2, etc. inhibitors when detecting inherited gene mutations in the adjuvant treatment of breast cancer allows for effective personalization of treatment and prevention strategies, improving the prognosis, quality, and life expectancy of patients.

Keywords: genetic studies, breast cancer, targeted therapy, prevention.

Значення генетичних тестувань у пацієнтів із раком молочної залози для виявлення груп ризику, обрання стратегії лікування і профілактики, прогнозування

С. В. Бусел

Вступ. Рак молочної залози (РМЗ) є одним із найпоширеніших злоякісних новоутворень у світі. Причиною 5,0–10,0% усіх випадків РМЗ є мутації деяких генів, тому своєчасна генетична діягностика уможливить здійснювати ефективну профілактику, обирати цільову терапію, оцінювати прогноз захворювання.

Мета. На основі аналізу опублікованих результатів досліджень з'ясувати значення генетичних тестувань у пацієнтів із раком молочної залози з метою обрання стратегії лікування і профілактики.

Матеріяли й методи. Пошук і аналіз джерел літератури здійснювали серед публікацій у відкритих базах даних PubMed/MEDLINE, SCOPUS, WEB of SCIENCE за ключовими словами: рак молочної залози, генетичні дослідження, лікування, профілактика.

Результати. Висвітлено перехід від зосередження уваги на генах BRCA1/2 до використання комплексних мультигенних панелей, а також роль генетичної діягностики у виборі персоналізованих стратегій лікування і профілактики РМЗ. Наголошено на важливости інтерпретації результатів генетичних досліджень, із акцентом на застосуванні таких тестів, як Oncotype DX, що допомагають передбачити користь від хіміетерапії та оцінити ризик рецидиву РМЗ. Проаналізовано прогнозну цінність застосування опитувальника «Інструмент оцінки ризику раку молочної залози» (Breast Cancer Risk Assessment Tool - BCRAT), який уможливлює оцінити ризик появи інвазивного РМЗ у жінки упродовж наступних п'яти років і до 90 років. Коротко розглянуто новітні діягностичні технології, такі як мультигенні панелі та рідка біопсія.

Розглянуто тактику і стратегію лікування і профілактики РМЗ із урахуванням результатів генетичного тестування. Наведено публікації щодо таргетної або цільової індивідуалізованої терапії, яка спрямована на відновлення ДНК у пацієнтів із генними мутаціями, що збільшує ефективність комплексного ад'ювантного лікування онкологічної хвороби. Описано приклади таргетної терапії, заснованої на відновленні ДНК за наявности мутацій генів BRCA1/2 та ін. Підкреслено, що інгібітор PARP Олапариб особливо ефективний для лікування пухлин, що містять патогенні варіянти в BRCA1, BRCA2 та PALB2, оскільки ці гени відіграють

основну роль у відновленні ДНК. Констатовано ефективність Алпелісібу в разі мутацій PIK3CA за ER/PR-позитивних варіянтів РМЗ. Наведено публікації щодо ефективности HER2-цільової терапії, включаючи Трастузумаб, Пертузумаб, Тукатиніб, Трастузумаб дерукстекан, для лікування HER2-позитивного або HER2-low РМЗ. Розглянуто роль інгібіторів CDK4/6, таких як Палбоцикліб, Рибоцикліб, Абемацикліб у цільовій терапії пацієнтів з позитивними аналізами на рецептори естрогенів (estrogen receptor - ER) та прогестерону (progesteron receptor - PR), тобто ER/PR-позитивного поширеного раку молочної залози. Обговорено роль цільової імунотерапії Пембролізумабом, який схвалено для тричі негативного метастазного або неоперабельного РМЗ, особливо, якщо він позитивний на ліганд до рецептора PD-L1, який є на поверхні клітин пухлини. Пембролізумаб також схвалений для лікування хворих із ранньою стадією тричі негативного РМЗ та високим ризиком рецидиву, використовується в поєднанні з хімієтерапією як неоад'ювантна курація перед операцією та самостійно після операції.

Проаналізовано профілактичні заходи, такі, як двобічна редукційна мастектомія, двобічна профілактична сальпінгоофоректомія, у жінок, які є носіями патогенних варіянтів BRCA1 або BRCA2, і у жінок зі значною сімейною історією РМЗ. Посилені протоколи спостереження рекомендовано для осіб, у яких виявлено патогенні варіянти, що включає частіші та розширені дослідження молочних залоз, такі, як мамографія та МРТ молочних залоз, починаючи з 30–35 років. Хімієпрофілактика, тобто застосування лікарських засобів, спрямованих на зниження ризику раку, наприклад інгібіторів ароматази, може бути розглянута для пацієнтів із гормоночутливим РМЗ.

Висновки. Генетичні тестування у жінок, хворих на рак молочної залози або з обтяженим сімейним анамнезом, уможливлюють виявляти групи ризику, визначати тактику і стратегію ад'ювантного лікування, обирати профілактичні заходи. Застосування інгібіторів PARP, HER2 та інших під час виявлення спадкових мутацій генів у ад'ювантному лікуванні раку молочної залози уможливлює ефективно персоналізувати стратегії лікування та профілактики, поліпшувати прогноз, якість і тривалість життя.

Ключові слова: генетичні дослідження, рак молочної залози, цільове лікування, профілактика.

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