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Review paper

Advancements in Emerging Molecular Approaches: Promising Diagnostic and Therapies Methods for Triple-Negative Breast Cancer (TNBC) Treatment

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Abstract

Background and Aim: This review explores recent advancements in molecular and cellular approaches for therapeutic interventions and diagnostic methods in Triple-Negative Breast Cancer (TNBC). It aims to investigate novel therapies targeting specific molecular pathways to transform TNBC treatment and improve patient outcomes.

Method: The methodology involves a systematic analysis of recent research findings, clinical trials, and developments related to molecular and cellular approaches in TNBC. A comprehensive literature review was conducted, encompassing relevant articles, studies, and clinical trial reports. The selected data were critically evaluated to extract valuable insights into emerging therapeutic interventions and diagnostic modalities for TNBC.

Results: The review consolidates findings from recent research and clinical trials, presenting a comprehensive overview of the current landscape of molecular and cellular approaches in TNBC. It synthesizes information on novel therapies targeting specific molecular pathways, highlighting their potential efficacy and impact on patient outcomes. Additionally, the review discusses the role of molecular techniques in early and accurate TNBC diagnosis, emphasizing the strides made toward personalized and targeted treatment options.

Conclusion: In conclusion, this review underscores the significant promise held by cutting-edge molecular and cellular approaches in shaping the future of TNBC management. The insights suggest a transformative potential for novel therapies, offering hope for improved treatment strategies and outcomes in TNBC patients. Furthermore, the integration of molecular techniques in the diagnostic landscape presents an exciting avenue for advancing personalized and targeted approaches, heralding a new era in the fight against TNBC.

Keywords: *Triple-Negative breast cancer, Molecular approaches, Diagnosis, Treatment*

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Introduction

Triple-negative breast cancer (TNBC) is a fast-growing type of breast cancer that does not have estrogen receptor, progesterone receptor, or human epidermal growth factor receptor-2. To effectively treat TNBC, diagnosing and categorizing the tumors is important. This helps decide the best treatment options and create personalized medications for each TNBC patient. Therefore, there is a vital need to develop fast and advanced technologies that can make TNBC diagnoses more accurate and efficient, in this case, molecular techniques.

- *Cancer*

Cancer is caused by mutations and abnormal cell growth resulting from various factors such as carcinogenic chemicals, viruses, bacteria, radiation, and hereditary factors. Other factors include exposure to pharmaceuticals, tobacco, sunlight, lack of breastfeeding, hormones, parasites, fungi, low-fiber diets, alcohol, bacteria, and herbs. The complexity of cancer makes it difficult to diagnose and treat effectively, making it the second leading cause of death worldwide. Men are more prone to prostate, lung, colon, rectum, and bladder cancer, while blood, brain, and lymph node cancers are more common in children. Breast and prostate cancer are the most common types of cancer among men and women, affecting the breast, lungs, colon, rectum, uterus, and thyroid [1], [2]. Recent advances in in-silico methods and molecular techniques have helped improve our understanding of cancer. This new information can lead to earlier diagnosis and better treatment for patients. Scientists have also uncovered how gene mutations and other genetic disorders cause cancer cells to form and develop. These findings can improve cancer treatment and reduce complications (Figure 1).

- *Breast Cancer*

In many countries, breast cancer is the most prevalent cancer in women and the leading cause of cancer-related deaths. One in eight women worldwide is at risk of developing breast cancer during their lifetime (Table 1) [3]. Breast cancer is a diverse disease with various biological and clinical characteristics. It can spread to other organs, such as bone, liver, lung, and brain, and become deadly in advanced stages. The hyperproliferation of ducts and long exposure to carcinogens can lead to benign tumors progressing into malignant and metastatic ones. Certain gene mutations and risk factors, such as age, family history, estrogen levels, and lifestyle, increase the risk for breast cancer. The BRCA1 and BRCA2 genes are associated with higher risks, and hormones and certain lifestyle factors can increase the risk of developing this disease. Mammography is an effective screening method for breast cancer, and MRI is a sensitive screening tool that can help diagnose invasive ductal carcinoma. Women are more likely to develop breast cancer than men, and about 25% of cases have a hereditary component [4]. Breast cancer can be classified into four main molecular groups based on the presence of hormones and proteins, including luminal A, luminal B, HER2-positive, and Triple-Negative Breast Cancer (TNBC). Luminal A tumor is the most common type and tends to grow slower than others. Luminal B cancerous tumor grows faster than luminal A and is more aggressive. HER2-positive breast cancer lacks ER and PR receptors and has human epidermal growth factor receptor 2 [5]. TNBC lacks estrogen, progesterone, and HER2 receptors.

Table 1. Possibility of Diagnosis or Death because of breast cancer in women of the US in periods of ten years.

Age of patients (10 years)	Diagnosed with invasive breast cancer	Death because of breast cancer
20	0.1% (1 in 1.479)	0.1% (1 in 18.503)
30	0.5% (1 in 209)	0.1% (1 in 2.016)
40	1.5% (1 in 65)	0.2% (1 in645)
50	2.4 % (1 in 42)	0.3% (1 in 310)
60	3.5% (1 in 28)	0.5% (1 in193)
70	4.1% (1 in 25)	0.8% (1 in 132)
80	3.0% (1 in 33)	1.0% (1 in 101)
Lifetime risk	12.8% (1 in 8)	2.6% (1 in 39)

- *Triple-Negative Breast Cancer (TNBC)*

Triple-negative breast cancer (TNBC) is usually aggressive and starts in the ducts of the breast. An estimated one million breast cancer cases are diagnosed worldwide each year, of which approximately 170,000 are of the TNBC phenotype. TNBC is a rare and aggressive form of breast cancer, affecting 13 out of 100,000 women annually. It is a heterogeneous disease, accounting for 10-20% of all invasive breast cancers [6]. Surgery is often the first choice for treating a large tumor, followed by chemotherapy to reduce the chance of cancer returning. Depending on the type of surgery and the characteristics of the tumor, radiation therapy may also be an option. However, surgery is a viable treatment option if the cancer has not spread to distant places. Research has shown that up to 80% of breast tumors from BRCA1 mutation carriers exhibit the TNBC phenotype. While the incidence of BRCA mutations is very low in all breast cancer subtypes (~5%), BRCA mutations are more common among individuals with TNBC (~20%). Given the lack of expression of well-known breast cancer antigens in TNBC, early detection is especially important for this type of breast cancer, as fewer molecular diagnostic methods are available. Epidemiological data indicate that TNBC is more prevalent in women under 40, and their survival time is shorter than other types of breast cancer, with 40% of these women passing away in the first five years after diagnosis [7]. Moreover, 46% of TNBC patients experience metastases in the brain and viscera, typically with an average survival time of 13.3 months after metastasis. Also, the average recurrence time in patients with TNBC is 51 months, while it is 29 months in patients with cancer other than TNBC. Triple-negative breast cancer (TNBC) is divided into six distinct subgroups, including basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), mesenchymal stem-like (MSL), immunomodulatory (IM), luminal androgen receptor (LAR) (Fig. 1) [8].

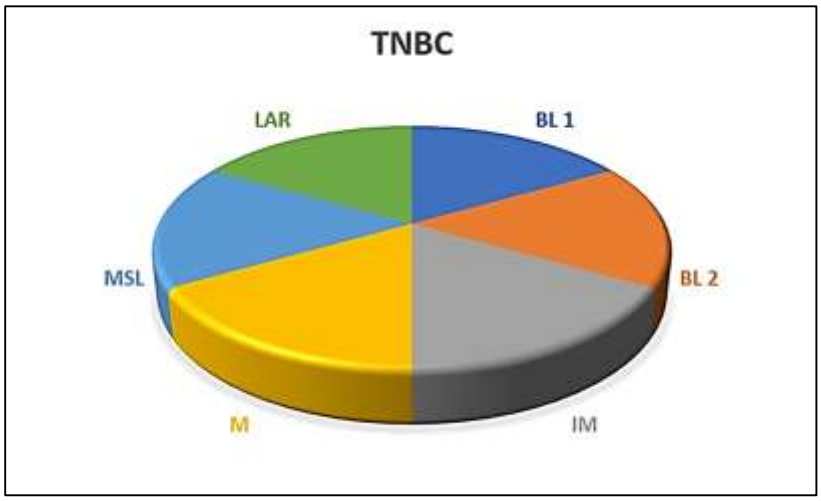

Figure 1. Schematic model showing the molecular heterogeneity of TNBC. Based on the expression profile, TNBC can be classified into distinct subtypes.
*LAR: luminal androgen receptor, MSL: mesenchymal stem-like, M: mesenchymal, IM: immunomodulatory, BL2: basal-like 2, BL1: basal-like 1

Methods

For this narrative review, we used the keywords Triple-Negative, breast cancer, diagnosis, and treatment to study all articles published since 2023. Our sources were PubMed and Scopus. The articles we examined enabled us to develop a conceptual scheme in triple-negative, based on the new approaches of antibodies and vaccines with high specificity. These findings have enabled us to reach the last diagnosis and treatment techniques for breast cancer, particularly for triple-negative patients.

Results

- Diagnosis Methods

The poor outcome of TNBC is because it tends to grow and spread quickly, varies a lot between patients, and is likely to come back after treatment. Researchers want to use advanced technology to study this type of breast cancer, understand how it develops, and find markers that can help predict a patient's chance of survival. At present, there are a few diagnosis methods based on molecular approaches, including Immunohistochemistry (IHC), Gene expression profiling, Next-generation sequencing (NGS), Fluorescence in situ hybridization (FISH), Breast Cancer Index (BCI), Biomarkers, and so on that will be discussed in the following.

Currently, a breast cancer diagnosis is achieved through a time-consuming two-step method consisting of imaging (mammography, ultrasound, and MRI of the breast) and immunohistochemistry (IHC). The lowest possible radiation dose in mammography should be employed to ensure it does not penetrate the breast tissues too deeply. A breast cancer diagnosis is made by observing calcifications (white spots), tumors, or masses. However, the main challenge lies in false negative and false positive results, which can directly impact the patient’s treatment outcome. Mammography diagnostic methods also carry certain risks, especially for individuals at a higher risk of developing cancer, such as those who carry the BRCA gene or have a family history of breast cancer. Ultrasound is another diagnostic method used when mammography fails to detect a mass. In contrast, if a sample is taken from the appropriate area and tested for cancer diagnosis, the mass can be identified using basic diagnostic methods. MRI is employed when a

patient has a high risk due to family history or mutations in the BRCA gene. However, one of the drawbacks of MRI is that it cannot accurately diagnose the type of breast cancer, only detect its presence. To ensure accurate results, the IHC test for breast carcinoma should consider the presence of biomarkers such as hormone receptors (progesterone receptor (PR) and estrogen receptor (ER)) and HER2 receptor markers. To ensure reliable results, IHC testing for ER and PR needs to be positive when the presence of cancer cells in the immune reaction is at least 1%, and the IHC test for HER2 should be followed up with fluorescent in situ (FISH) to avoid any false positive or false negative diagnosis that can affect the treatment plan.

Some recent studies have discovered that TNBC commonly has mutations in the TP53 gene and problems with genes related to the immune system's response to cancer. Furthermore, the PIK3CA gene and DNA repair pathways often have mistaken, usually harmful alterations in TNBC. Simply put, these findings suggest that patients with breast cancer with a particular genetic marker called PD-L1 or who struggle with DNA repair might have access to personalized treatments. Moreover, scientists have used advanced NGS technology to study large genomes and discover significant markers in TNBC that are important in medicine. Some examples of these markers are AURKA, MYC, and JARID2 mutations. Moreover, research using NGS to examine variations related to different ethnic groups discovered that having too much EZH2, changes in BRCA1, and a specific mutation in BRCA2 (specifically, the removal of the sequence AAGA) might indicate the presence of TNBC at the molecular level in certain individuals [9].

The Breast Cancer Index test examines the behavior of 11 genes to foresee the likelihood of hormone-receptor-positive breast cancer reappearing within 5 to 10 years after diagnosis. The test can assist women and their doctors in determining whether it would be helpful to continue hormonal therapy for an additional five years (totaling ten years). The Breast Cancer Index gives two pieces of information. It tells us how likely the cancer will return 5 to 10 years after its diagnosis. It also tells us if a woman should take hormonal therapy for ten years and if it will help her.

MammaPrint is a test that is used to analyze breast cancer. The 70-gene signature test is a method that measures the activity of 70 specific genes in early-stage breast cancer. It helps determine the likelihood of cancer coming back in the future by giving a simple answer of either low or high risk for recurrence. The MicroarRAy PrognoSTics in Breast CancER (RASTER) trial found that patients at low risk for breast cancer had a very small chance of cancer returning to other parts of their body. After five years, 97. 0% of these patients did not experience a recurrence; after ten years, 93. 7% did not experience a recurrence. In a study by [10], out of the 1347 samples that were tested, 607 (which is 45%) did not pass the quality control after RNA extraction. Of all the patients, 658 (49%) were included in the survival analysis. After five years, 94. 0% of those at low risk were recurrence-free, compared to 91. 6% of those at high risk. This means that being at low risk reduces the chance of recurrence by 6. 5% after ten years. The statistical analysis showed that this difference in risk is significant, with a p-value of 0. 017 After ten years, 91. 3% of those at low risk were recurrence-free, compared to 84. 8% of those at high risk. The results from the multivariable models show that the tumor stage mostly influences the risk of a negative outcome (hazard ratio) and whether there is any involvement of the lymph nodes. Over five years, the hazard ratio for tumor stage is 3. 89 (with a confidence interval of 1. 97-771), and for nodal status is 1. 73 (with a confidence interval of 0. 91-321). After considering the different risk levels in patients, the MammaPrint HRs (hazard ratios) remain steady, with values slightly lower than 2. 0 after the initial three years.

Advancements in molecular technologies have discovered various biomarkers studied to help

diagnose diseases, predict outcomes, understand drug resistance, and develop treatments. Finding biomarkers could help solve the issue of drug resistance, which is a difficult problem in treating breast cancer; furthermore, Biomarkers are important for detecting, understanding, and controlling breast cancer promptly. Moreover, as mentioned previously, biomarkers help diagnose the disease, predict its outcome, and guide treatment decisions [11]. Scientists have considered using a certain type of protein in the body as a biomarker to identify and study breast cancer; one is Serum apolipoprotein C-I (apoC-I). Serum apolipoprotein C-I (apoC-I) has shown promising results in predicting and identifying triple-negative breast cancer (TNBC). It can differentiate between cases of TNBC and non-TNBC by measuring higher levels of ApoC-I mRNA and protein expression in TNBC patients compared to non-TNBC patients and healthy individuals [12].

Another diagnosis method that is based on molecular technique is Biosensors. Additionally, a biosensor, which consists of a biological receptor, a detector, and a signal converter, can be used to identify and analyze a wide range of biological samples, such as enzymes, antigens, antibodies, and nucleic acid components (DNA, RNA, microRNAs). Biosensors can be divided into several categories based on their transducer elements, such as electrochemical, optical, piezoelectric, and thermal sensors [13]. Nano biosensors, which are biosensors combined with nanoparticles and transducers that enhance the signaling and biological transmission process, have also been developed for this purpose; for example, the zinc oxide (ZnO)-choline oxidase (ChOx) nano biosensor can detect the presence of choline in TNBC samples. This diagnostic pathway utilizes a data analysis tool with 770 genes to classify breast cancer based on molecular subgrouping.

Overall, these molecular methods have several advantages in detecting TNBC than regular (traditional) methods. Consequently, gene expression profiling can identify the molecular subtypes of TNBC based on the expression levels of many genes, which can provide a more accurate and comprehensive characterization. Ditto, detecting genetic mutations in the tumor genome that may be relevant to the development and progression of TNBC gives information that can be used to guide treatment decisions and monitor the response to therapy. Additionally, Molecular methods can be performed on small amounts of tissue, including samples obtained through minimally invasive procedures such as fine-needle aspiration or core needle biopsy. This can reduce the need for more invasive surgical procedures and improve patient outcomes. Unfortunately, there are a few problems with using molecular diagnosis methods for triple-negative breast cancer (TNBC). These include cost, availability, the quality of the samples used, and how helpful the results are in a clinical setting. Therefore, medical tests such as gene analysis and next-generation sequencing sequencing can be expensive, and insurance or healthcare systems may not cover the cost of these tests. This can make it hard for people in poorer countries to take these tests. Simply put, some healthcare centers or areas may not have the necessary tools, knowledge, and facilities to use molecular diagnosis methods. Places where it is difficult for people to use technology. Furthermore, the process of identifying diseases using molecules requires high-quality tissue samples. Sometimes, it takes work to obtain these samples. This can occur if the tumor is small or the person has already been treated.

- *Treatment Methods*

Currently, the main treatments for treating Triple-negative Breast Cancer (TNBC) are surgery, radiation therapy, chemotherapy, specifically anthracycline- and Taxane-based regimens, which are aggressive and have undelighted patient outcomes [14]. Chemotherapy may make the patient feel tired, lose the desire to eat, feel sick, have problems with bowels like constipation or diarrhea, lose hair, have sores in their mouth, and have issues with skin and nails. Some people may find it difficult to focus or remember things. Additionally, there may be impacts on the nerves, muscles,

and hearing. The person's chance of getting infections will also be higher. So, there is a vital demand for targeted therapies for treating TNBC.

Ongoing molecular therapies against TNBC include PARP inhibitors, Immunotherapy, Targeted therapies, Antibody-drug conjugates (ADCs), and Cyclin-dependent kinase (CDK) inhibitors.

Lately, a new type of molecule called PARP inhibitors has become a common treatment for patients with TNBC and a mutation in the genes BRCA1 or BRCA2. Currently, two drugs, Olaparib and Talazoparib, have been permitted for TNBC. They were approved after two big studies showed that they could help patients live longer without cancer worsening compared to chemotherapy. The safety of the treatment was acceptable with the help of supportive therapies and adjustments in the dosage. Other PARP inhibitors are being studied, including Rucaparib and Veliparib [14]. Overall, Olaparib and Talazoparib are given alone as a treatment for metastatic TNBC with a BRCA 1 or 2 gene mutation. This is based on what was found in two trials [15] and [16].

Having researched the clinical trials on clinicaltrials.gov, there are several ongoing trials for immunotherapy of TNBC; furthermore, immunotherapy treatment for TNBC has been studied a lot in the past ten years. One analysis by [17] released that most of the trials (84%) focused on a type of immunotherapy called PD-(L)1 inhibitor. Out of these trials, only 13 were studied using PD-(L)1 inhibitors alone, while the rest combined them with other TNBC treatments. Many trials are happening for both early and advanced TNBC, showing that immunotherapy can be used in different stages of the disease. Additionally, more trials are starting to test the best time to use immunotherapy and how it affects biomarkers.

Scientists have noticed that some patients with triple-negative breast cancer (TNBC) have a certain protein called androgen receptor (AR) in their cancer cells. This means that blocking the action of androgen hormones might be a promising way to treat TNBC. The new drugs that stop the activity of the AR protein have created new treatment options for breast cancer patients with AR-positive triple-negative breast cancer cells. Enzalutamide is an androgen receptor inhibitor that has appeared guaranteed in early-stage inquiries about treating TNBC.

An antibody-drug conjugate (ADC) is a type of medicine used to treat cancer. It consists of a special protein that attaches to cancer cells and a powerful drug that can kill these cells. A special chemical connects the two parts. This treatment is becoming more popular in cancer treatment. New types of drugs called sacituzumab govitecan (IMMU-132) and trastuzumab deruxtecan (DS-8201a) for advanced breast cancer are being tested on patients in the final stages of clinical studies, including those with triple-negative breast cancer.

Scientists are studying CDK inhibitors concerning TNBC as possible treatments that specifically target the cancer. CDKs are a group of proteins that help control the process of cell division. When they don't work properly, they can lead to cancer. In TNBC, scientists are studying CDK inhibitors to stop cell growth and prevent cancer cells from multiplying. Currently, numerous drugs are being used against TNBC, including Palbociclib, Ribociclib, and Abemaciclib. Additionally, these drugs are CDK4/6 inhibitors that have been studied in clinical trials for TNBC.

Conclusion

Triple-negative breast cancer (TNBC) could be a troublesome and complex frame of breast cancer. It is aggressive, meaning it develops and spreads rapidly. Patients with TNBC can be exceptionally distinctive from each other, making it troublesome to find treatments that work for everybody. TNBC is additionally likely to come back after treatment. To fathom these issues, researchers have used advanced molecular technology to learn about TNBC and develop better ways to diagnose

and treat it. Progressed strategies like immunohistochemistry, gene expression profiling, next-generation sequencing, and biomarker-based tests have supported finding triple-negative breast cancer (TNBC) and understanding its distinctive sorts. These strategies can assist specialists in making more exact and personalized analyses, which can help arrange and screen medications. However, molecular diagnostic methods have a few issues, like cost, availability, test quality, and convenience for therapeutic purposes. We ought to guarantee these imperative devices are effectively available and cheap, particularly in places with constrained assets. When treating TNBC, specialists have traditionally utilized strong treatments like surgery, radiation, and chemotherapy. In any case, these treatments can cause genuine side impacts and make individuals feel unwell. Modern sorts of drugs called targeted therapies have been created. These incorporate PARP inhibitors, immunotherapy, antibody-drug conjugates, and CDK inhibitors. These treatments offer trust for superior choices. These medications have the potential to decrease negative side effects. Also, progressing ponders and trials are still being conducted to learn more about TNBC and progress treatment choices. Immunotherapy appears to have a part of its potential, particularly with PD-(L)1 inhibitors and utilizing them with other medicines. Additionally, discovering that the androgen receptor (AR) can be focused on in certain cases of triple-negative breast cancer (TNBC) presents conceivable outcomes for tailored treatments. In the future, combining molecular tests with particular treatments has the potential to make strides in the viewpoint and quality of life for individuals with TNBC. As we proceed to study and learn, it is exceptionally imperative to bargain with the issues of making, beyond any doubt, that everybody can utilize and manage these unused advancements in medication so that patients worldwide can benefit from them.

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Conflict of interests

The authors declare that there are no competing interests.

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