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REVIEW ARTICLE

# The Promise of Critical Biomarkers: An Optimistic Future in Breast Cancer Therapeutics

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ABSTRACT: In a woman's lifetime, there is a roughly 1 in 8 chance that she will contract breast cancer. Moreover, if she has a close relative with breast cancer, these chances escalate dangerously due to the passing on of genes with a high risk of mutation. Although women are more likely to develop this disease, men can succumb to breast cancer as well. This life-threatening disease is often hereditary or caused by a gene mutation. Fortunately, biomarkers offer insight into the prognosis and reactiveness a breast cancer patient may have. Biomarkers are genes, proteins, or other occurrences in the genome linked to a disease's etiology or vulnerability, such as cancer. They uniquely provide a predictive ability to help assess how a breast cancer patient may react to certain treatments. Recent studies on this topic include researching populations to discover which genes can potentially be biomarkers. Further analysis dives into certain biomarkers and their importance in breast cancer treatments. In this detailed review, genomic biomarkers found to have a connection with breast cancer are discussed, as well as how they will essentially pave the way for critical treatments, insights, and preventative tactics in oncology.

KEYWORDS: Biomedical and health sciences; Genetics and molecular biology of disease; Breast cancer; Metastasis; Diagnostic biomarkers.

## Introduction

The female breast is far beyond complex. It comprises glandular tissue, ducts, lobes, lobules, lymph nodes, and connective tissue1 strategically arranged into bundles (Figure 1).

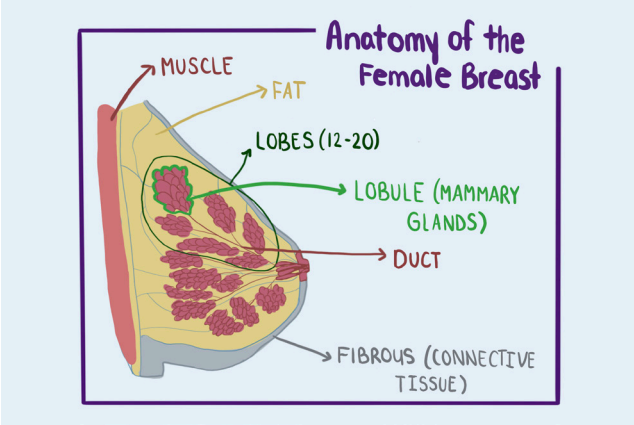


**Figure 1:** A schematic diagram of the female breast entails muscle, fat, lobes, ducts, fibrous tissue, and the mammary glands–these parts of the breast work together to produce milk during motherhood. Breast cancer mainly originates in the lobules, ducts, and more specifically, epithelial cells that line these areas.

Due to many intricate processes in the breast, cells may start to experience unregulated divisions, causing a tumor to form. Uncontrollable cell division is the epitome of cancer, but each cancer entails its own set of unique characteristics. To truly understand the specific features of the breast cancer type, specific biomarkers provide patterns to help physicians determine which treatments they should utilize. Biomarkers also have the potential to lend insight into the future progression of the disease. In this Review, genetic markers are intensively discussed in the subject of breast cancer. Knowing the etiology contributing to this cancer before understanding each biomarker and its potential is key. The set of causes for this intricate disease are deduced to sex, aging, and family history.[1,2]

According to The National Cancer Institute's 2017-2019 data, about 13% of women will have cancer throughout their lifetime.[3] Because women have many more breast cells than men, women have a higher risk of developing breast cancer. Breast cells are constantly undergoing processes involving intense contact with estrogen and progesterone, which regulate cells located in the breast tissue.[4] This intense amount of contact increases the likelihood of a mistake occurring in the process. Additionally, as women age, the likelihood of cancer-causing mutations increases because of slower responsiveness. The delay in preparedness to fight decreases the chances of the body being able to restore the damage inflicted, especially before it worsens.[5] Furthermore, although breast cancer cannot be directly inherited through family history, mutated genes that occur in the BRCA1 and BRCA2 genes are likely to be passed down to heighten the risk of breast cancer.[6] With this information in hand, being aware of a familial history of breast cancer or circumstances increasing risk is very helpful in making one acquire a mammogram or biomarker testing for screening.

In chemistry, pH indicators indicate whether a solution is an acid or a base by expressing its color. Just as a pH indicator identifies whether a compound is an acid or a base, biomarkers reveal various functions in the body and whether any are functioning normally or atypically.[7] This is especially significant in confirming the presence of cancer in the body and what type it falls under. On the subject of biomarkers, two different subtypes apply within the context of breast cancer. First, predictive biomarkers reference the reactions that may occur regarding therapies.[8] These biomarkers benefit physicians by allowing them to choose which therapies to administer with the clinical outcome in mind. On the other hand, the second class of genomic markers is known to be prognostic. These biomarkers



DOI: 10.36838/v6i7.11

offer a vision of a patient's future progression of the cancer they have and provide information about the outcome and fatality of the disease.[9]

Biomarker testing is increasingly important in helping physicians determine the cancer diagnosis, most beneficial therapeutics, future progression of the disease, and having clear insight into the responses that one's body may have to certain treatments. Furthermore, biomarkers are essential in developing advanced treatments that will lessen the severity of the cancer outcome. This Review expands upon three specific biomarkers that provide these abilities. They are especially useful in making life-saving decisions regarding innovations in therapeutics or insight into predicting the cancer's future prognosis.

## Discussion

### *Breast cancer gene 1 (BRCA1) and Breast Cancer Gene 2 (BRCA2)*

#### *BRCA1 and BRCA2 as Prognostic Markers:*

In hereditary breast cancer, the BRCA1 and BRCA2 genes are by far the most frequently mutated, and they are noted to be responsible for about 3% of all breast cancers.[10]

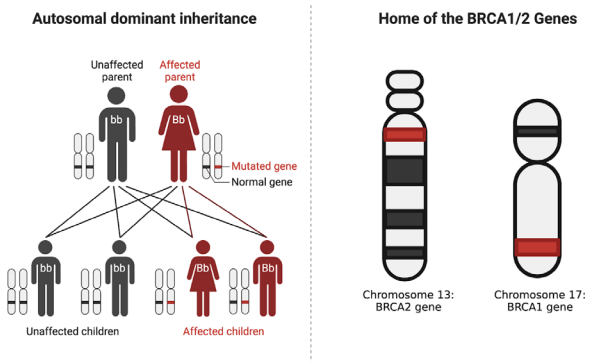


**Figure 2:** Traces the autosomal dominant inheritance patterns of the BRCA1/2 genes and their locations on human chromosomes. The figure was created with BioRender.

BRCA1/2 is primarily the cause of familial history being a risk for the development of breast cancer. Figure 2 depicts that each child from a couple with one parent carrying a BRCA1/2 mutation in either of these two genes has a 50% chance of inheriting the mutation. To understand BRCA1/2's role as a biomarker, it is important to consider that these genes normally prevent one's body from developing cancer through their critical role as a tumor suppressor; this job is primarily responsible for regulating cell divisions. However, when mutated, these genes do not function as effectively as before and, therefore, increase the risk of one acquiring breast cancer.[11] According to a collaborative study done by the Department of Oncology and various other scientific departments in France, research was conducted to uncover the clinical outcome of BC patients with BRCA1/2 mutations. Out of the cohort of 925 patients, exactly 171 of them carried the BRCA1 mutation and 95 had the BRCA2 mutation.[11] Furthermore, 68% of the patients with BRCA1 mutation had triple-negative breast cancer (TNBC) whereas 19% of BRCA2 carriers and 24% of non-carriers ended up with TNBC.[11] Mutations in the BRCA1 gene typically lead to triple-negative breast cancer (TNBC), which is a type of breast cancer where the patient tests negative on a total of 3 tests (estrogen [ER], progesterone [PR], and HER2).[12] In contrast, mutations in the BRCA2 gene usually result in tumors that test positive for estrogen and progesterone. Triple-negative breast cancer is by far the deadliest of all breast cancers and is associated with a much poorer and complicated prognosis than other breast cancers.

With the knowledge that BRCA1 and BRCA2 are biomarkers, it is essential to understand their role in projecting cancer prognosis. It aids beneficially in setting the stage for advanced treatments and therapeutics. A recent study found that BRCA1/2 over-expression was detected in breast cancer tissues while absent in normal tissues.[13] This over-expression of BRCA1/2 is linked with shorter survival rates and a worse prognosis.[13] Although this topic is very controversial due to different findings in previous studies, BRCA1 as a prognostic marker for predicting cancer prognosis is a breakthrough and should be explored further.

#### *BRCA1 and BRCA2 as Predictive Markers for Therapies:*

In the recent couple of years, studies have emerged releasing BRCA1/2's predictive potential for breast cancer. But, even with this limited data on how this biomarker ties into a probable response of a patient to a particular therapy, recent studies have been reassuring. BRCA1/2 has demonstrated a response to poly(ADP-ribose) polymerase (PARP) and platinum-chemotherapy for patients with metastatic breast cancer.[14] Metastatic patients who were carriers of BRCA1/2 demonstrated to have a much lengthier progression-free survival and other positive characteristics when they used PARPi olaparib compared to conventional chemotherapy.[14] Receiving this response in therapy is a great step towards developing new treatments for breast cancer, specifically BRCA1/2 carrier patients with metastatic breast cancer. Despite this, there is still much to learn about BRCA1/2 and its predictive ability for breast cancer.

### *Estrogen Receptor (ER) and Progesterone Receptor (PR)*

#### *ER and PR as Prognostic Markers:*

Estrogen receptor (ER) is by far the most useful and clarifying protein for researchers and it is famous for its dual role as a predictive and prognostic biomarker. This popular transcription factor occurs in diverse organs around the body; it includes tissues such as small areas of the reproductive glands and a large amount of the breast where it regulates divisions and carries out significant tasks.[15] Since ER expression is a recurrent characteristic among the several breast cancers, it is utilized as a guide for many treatments.[16] Importantly, the variation in expressions of ER can mark the difference between two types of tumors, ER-positive and ER-negative. This estrogen receptor status is commonly identified using immunohistochemistry (IHC), a method in the laboratory where tests are conducted on tissue specimens.[17] IHC is typically used to discover known biomarkers that are present in the sample and signal toward specific types of breast cancer. Once the tumor is identified after the estrogen levels are observed, researchers can better understand the clinical outcome due to this biomarker's prognostic ability. In primary breast cancer, about 75% of them are established as ER-positive.[18]

This estrogen receptor status was found to have the most positive clinical outcome with ER-positive breast cancer patients in a 2022 study in Ethiopia with a survival rate of 41.51% after a 6-year follow-up.[19] Meanwhile, the ER-negative receptor status of breast cancer had a 21.01% survival rate at the time of the 6-year follow-up with the patients.[19] Therefore, those diagnosed with ER-negative breast cancer are likely to have a worse prognosis than ER-positive breast cancer patients, considering the mortality rates.

The other hormone receptor associated with ER is the progesterone receptor (PR). This protein-coding receptor is known for its role in balancing the effects of progesterone on the body.[20] Within the mammary gland, 15-30% of luminal epithelial cells contained both ER and PR, while they were absent in other areas of the breast.[21] It is increasingly important to look at biomarkers when they come into play with each other, specifically the two hormone receptors: ER and PR. The survival rate of women with ER+/PR-, ER-/PR+, and ER-/PR- tumors was notably less compared to women with ER+/PR+ tumors.[22] This relationship demonstrates that the hormone receptor-positive patients have the most favorable prognosis. Nevertheless, despite their PR status, ER-positive patients still have a more positive clinical outcome. Without hormone receptors, breast cancer tends to have much faster growth and is not able to be treated with hormone therapy.

***ER and PR as Predictive Markers for Therapies:***

When it comes to employing certain therapeutics, ER receptors play an important role in acting as a predictive biomarker by providing scientists with more insight into which therapies will be most effective on cancer. ER status primarily helps those patients being treated with hormone therapy for the selection of selective estrogen receptor modulators (SERMS) or aromatase inhibitors (AIs). SERMS such as tamoxifen are effective by inhibiting the effect of estrogen on breast tissue. In contrast, AIs like anastrozole and letrozole block the aromatase enzyme to prevent estrogen from being produced (specifically for women after menopause).[23] Recently, selective estrogen receptor degraders (SERDS) have become a novel therapeutic approach for breast cancer which have the potential to be more effective than SERMS. SERDS bind to the estrogen receptor and cause it to lessen its protein expression through its deterioration.[24] However, this therapeutic is still under investigation for its implications and tangible patient outcomes. As shown previously, the estrogen receptor is a very significant factor in selecting which treatments will be optimizable for the cancer type. When it comes to PR, there is still much to be learned. Selective progesterone receptor modulators (SPRMs) have risen as a viable therapeutic for PR+ breast cancer that targets PR signaling pathways to improve clinical outcomes.[25] Studies are torn across whether it better responds to hormonal therapy: therefore, more research should be conducted to understand this complex biomarker fully.

***Human epidermal growth factor receptor 2 (HER-2)***

***HER-2 as a Prognostic Marker :***

Interestingly, HER-2 is expressed in an average of 25% of breast cancers.[26] It derives from the epidermal growth factor family which controls essential processes like cell proliferation, differentiation, and durability (Figure 3).[26] This protein's expression is examined through the use of immunohistochemistry (IHC), similar to ER and PR. Also, other ways were found to efficiently test the levels of HER-2 such as the HerceptTest™, Fluorescence *in situ* hybridization (FISH), and HER2/neu (4B5) rabbit monoclonal primary antibody.[27] In HER-2 over-expression, the FISH test was more reliable.[28]

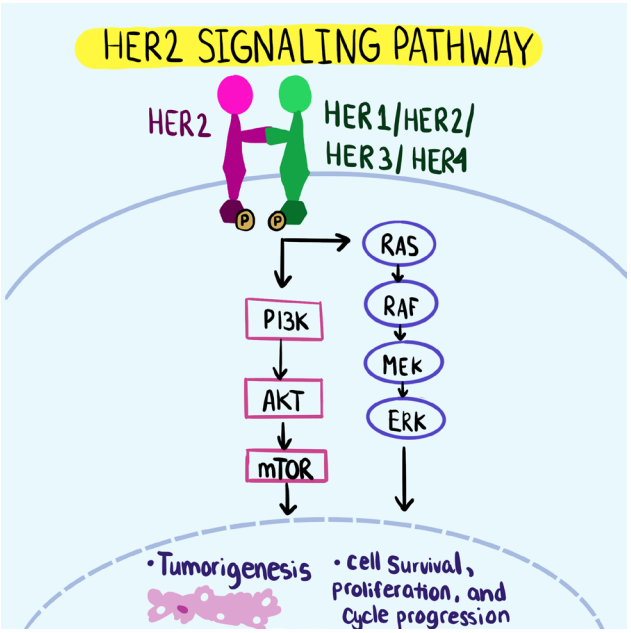


**Figure 3:** EGFR, HER-2, HER-3, and HER-4 activate RAS-GTP and PI3K signaling pathways and then send signals down to promote active transcription of genes involved in cell cycle proliferation, growth, and differentiation. Adapted from "HER2-positive breast cancer and tyrosine kinase inhibitors: the time is now" by Schlam and Swain, 2021.[29]

As a prognostic biomarker, HER-2 demonstrates vital information. HER-2 is amplified in about 15-30% of breast cancers and is an arising factor in various other cancers as well.[30] Breast cancer patients with over-expression of HER-2 tend to have a poorer prognosis than other breast cancer types. In a study that defined breast cancer survival through biomarkers, the cumulative survival for HER2 over-expression and triple-negative breast cancer was the lowest compared to the other cancers at 60 months.[31] HER-2 over-expression, also known as HER-2-positive breast cancer tends to have more of an aggressive prognosis with the likelihood of tumorigenesis compared to HER-2-negative breast cancer as shown in Figure 3. Additionally, HER-2 over-expression was associated with higher mortality and shorter disease-free survival (DFS).[28] Due to its predictive ability, HER-2-positive patients are treated with HER-2 targeted or anti-HER-2 therapies which has had a drastically positive impact on the prognosis.[28]

Conversely, HER-2 negative analysis studies showed potential in predicting prognosis. In a very recent meta-analysis, HER-2-low expression was found to be a prognostic indicator of longer DFS in the sample of this study and an improvement in overall survival in patients with advanced breast cancer. It is also important to note that hormone receptor (HR) positive patients had consistent DFS despite the HER-2 status.[32] In


DOI: 10.36838/v6i7.11

HR-negative patients, there was a more threatening prognosis when HER-2 status was low instead of zero.[32]

***HER-2 as a Predictive Marker for Therapies:***

Currently, HER-2 is used as a predictive marker for specific anti-HER-2 therapies such as trastuzumab, pertuzumab, lapatinib, neratinib, and trastuzumab emtansine (T-DM1). To demonstrate HER-2's predictive ability, it is important to dive into the types of therapy.

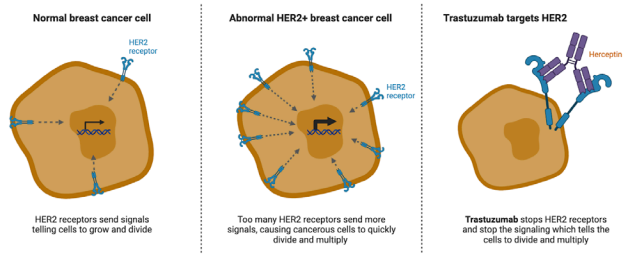


**Figure 4:** Exemplifies the HER2-targeted treatment Trastuzumab's therapeutic potential on an abnormal HER2+ breast cancer cell. The figure was created with BioRender.

Trastuzumab is a HER-2 targeted therapy that aims to treat early HER-2+ breast cancer.[33] This treatment blocks HER-2 to prevent over-expression and lessen the risk of poor prognosis as shown in Figure 4. In a detailed study, trastuzumab therapy was extremely beneficial in reducing the mortality rate of patients by 20% after being checked up on after 30 months.[34] In addition, when added to traditional chemotherapy, it had a great ability to help metastatic breast cancer patients with HER-2 overexpression.[34] Furthermore, studies suggest that if HER-2 expression is measured to be declining 2-4 weeks after the employment of trastuzumab therapy, it is a sign of progression-free survival.[35] In this case, HER-2 data is clinically essential in providing data on whether the patient responds to treatment. On top of monoclonal antibodies such as trastuzumab, recent studies have proposed that tyrosine kinase inhibitors (TKIs) can block signaling pathways activated by HER-2 over-expression.[36] In combination with other therapies, these novel therapies have the potential to improve breast cancer prognosis of HER2-positive breast cancer. Therefore, HER-2 is a critical biomarker for carrying out therapies for HER+ breast cancers.

## Conclusion

Breast cancer affected about 2.3 million people and took the lives of over 685,000 in 2020, causing it to be one of the most prevalent cancers across the globe.[37] To combat these immense mortalities, biomarkers are setting the groundwork for precision therapies and treatments. Not only are these genomic markers paving the way for these therapeutics, but they are aiding physicians in predicting future prognosis and treatment responses of patients diagnosed with breast cancer. BRCA1/2 can be tracked across generations and utilized as a tactical biomarker for acquiring genomic testing to assess whether one is a carrier or not. However, there is still much to learn about its predictive ability. Estrogen receptor (ER), known for its richness in information, acts as a predictive biomarker for breast cancer through responses to SERMs and AIs, and it sheds light upon cancer prognosis through its hormone receptor status. On the other hand, progesterone receptor (PR), in combination with ER, helps gain a deep understanding of future prognosis. However, there is still much to learn about its predictive ability. HER-2 possesses exceptional predictive ability with anti-HER-2 therapies on top of being a great prognostic biomarker for HER-2 over-expression and triple-negative breast cancer. Unfortunately, many studies that are centered around biomarkers do not reach a clear conclusion or ability to generalize to a larger sample. To make sure that sufficient treatments that will help breast cancer patients are developed, more biomarker studies are greatly needed, especially with larger samples and heterogeneity of breast cancer types. Biomarkers are present in other cancers besides breast cancer, so research must be carried out in different fields of cancer. Furthermore, more research on how these biomarkers interact with and affect each other is greatly needed. After all, biological processes happening in the human body are very complex and many factors affect these biomarkers and the prognosis of these cancer types.

## Acknowledgment

I would like to greatly thank Dr. Kif Liakath-Ali and Adrian Bebenek for providing me with guidance in this intensive Review. I appreciate the mentorship and feedback that they gave me while working on this paper. I would also like to give thanks to Dr. Shad Ahmad and Dr. Makiko Ogino-McElligot for fueling my interest and inspiring me greatly on this complex and novel topic of genetic markers. This research was conducted under the Indigo Research Program.

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DOI: 10.36838/v6i7.11