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Review

Oncogenes as Diagnostic Biomarkers in Breast Cancer: A Review of Molecular Detection and Clinical Utility

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Abstract

Breast cancer management has been revolutionized by the identification of key oncogenes which serve as critical diagnostic and prognostic biomarkers. These molecular alterations influence tumor behavior, treatment response, and patient outcomes, enabling personalized therapeutic strategies. This review comprehensively examined the most prominent oncogenes—HER2, PIK3CA, MYC, and BRCA1/2—implicated in breast carcinogenesis, the technologies used for their detection, and their implications for precision oncology. HER2 amplification, found in 15-20% of breast cancers, is associated with aggressive disease but responds well to targeted therapies like trastuzumab. While IHC and FISH remain standard detection methods, emerging technologies such as NGS improve sensitivity. PIK3CA mutations, common in HR+ tumors, drive therapy resistance but can be targeted with PI3K inhibitors, though clinical responses vary. The MYC oncogene promotes tumor proliferation and poor prognosis, but its therapeutic targeting remains challenging due to its complex role. BRCA1/2 mutations significantly increase hereditary breast cancer risk, particularly in TNBC and HR+ subtypes. PARP inhibitors have shown remarkable efficacy in BRCA-mutated cancers, highlighting the importance of genetic testing. Despite these advances, challenges such as tumor heterogeneity, assay standardization, and biomarker validation persist. Future directions include multi-omics integration, liquid biopsy development, and AI-driven diagnostics to refine precision oncology approaches.

Keywords:

Breast Cancer
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1. INTRODUCTION

Breast cancer remains one of the most prevalent malignancies worldwide, accounting for a significant proportion of cancer-related morbidity and mortality among women [1]. Despite advancements in early detection and treatment strategies, the heterogeneity of breast cancer poses challenges in diagnosis, prognosis, and therapeutic decision-making [2]. In recent years, molecular biomarkers have emerged as critical tools in refining breast cancer classification, enabling personalized treatment approaches, and improving patient outcomes [3]. Among these biomarkers, oncogenes—genes with the potential to cause cancer when mutated or overexpressed—have garnered substantial attention due to their pivotal role in tumorigenesis and disease progression [4].

The identification and validation of oncogenes as diagnostic biomarkers have revolutionized breast cancer management by providing insights into tumor biology, predicting therapeutic response, and identifying high-risk patients who may benefit from targeted therapies [5]. Oncogenes such as HER2, PIK3CA, MYC, BRCA1, and BRCA2 are frequently dysregulated in breast cancer and have been extensively studied for their clinical utility [6]. For instance, amplification of the HER2 oncogene is a well-established biomarker that guides the use of HER2-targeted therapies like trastuzumab, significantly improving survival in HER2-positive breast cancer patients [7]. Similarly, mutations in PIK3CA, a key regulator of the PI3K-AKT-mTOR pathway, have been implicated in resistance to endocrine therapies, necessitating the development of PI3K inhibitors to overcome treatment resistance [8].

Molecular detection techniques, including next-generation sequencing (NGS), polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH), and immunohistochemistry (IHC), have facilitated the precise identification of oncogenic alterations, enabling their integration into clinical practice [9]. These technologies not only enhance diagnostic accuracy but also allow for the monitoring of minimal residual disease and early detection of relapse [10]. Furthermore, liquid biopsy-based approaches, such as circulating tumor DNA (ctDNA) analysis, offer a non-invasive means to assess oncogene mutations in real-time, providing dynamic insights into tumor evolution and treatment response [11].

Despite these advancements, challenges persist in the standardization of oncogene testing, interpretation of molecular findings, and accessibility of biomarker-driven therapies across diverse populations [12]. Discrepancies in assay sensitivity, tumor heterogeneity, and clonal evolution may influence the reliability of oncogene-based diagnostics, necessitating rigorous validation in large-scale clinical trials [13]. Additionally, the cost and infrastructure required for advanced molecular profiling limit the widespread adoption of these technologies in low-resource settings, highlighting the need for cost-effective and scalable detection methods [14].

This review comprehensively examined the role of oncogenes as diagnostic biomarkers in breast cancer, focusing on their molecular detection methods and clinical utility. We discussed the most prominent oncogenes implicated in breast carcinogenesis, the technologies used for their detection, and their implications for precision oncology. Furthermore, we addressed current challenges and future directions in the field, emphasizing the need for biomarker-driven clinical trials and equitable implementation of molecular diagnostics in breast cancer care.

2. MATERIALS AND METHODS

This comprehensive review employed a rigorous systematic approach to evaluate the current evidence regarding oncogenes as diagnostic biomarkers in breast cancer, with particular emphasis on molecular detection methodologies and clinical applications. The methodology was designed to ensure maximal coverage of relevant literature while maintaining scientific rigor and reproducibility.

2.1. Search Strategy and Data Sources

An exhaustive literature search was conducted across online databases including PubMed/MEDLINE, Scopus, Web of Science, Embase, and Cochrane Library to identify pertinent studies published until April 2025. The search strategy incorporated a combination of controlled vocabulary terms (MeSH in PubMed, Emtree in Embase) and free-text keywords to optimize sensitivity and specificity. Key search terms included: "oncogene," "proto-oncogene," "tumor suppressor gene," "breast neoplasms," "biomarkers, tumor," "molecular diagnostic techniques," "gene expression profiling," "next-generation sequencing," "liquid biopsy," "circulating tumor DNA," and "precision medicine."

Boolean operators (AND, OR, NOT) were strategically employed to create complex search strings that captured all relevant permutations of these concepts. The search combined terms for oncogenes ("HER2," "PIK3CA," "MYC," "BRCA1," "BRCA2"), diagnostic applications ("early detection," "screening," "prognosis," "predictive value"), and detection methods (e.g., "PCR," "FISH,"

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"NGS," "microarray"). No geographical restrictions were applied, but results were limited to English-language publications.

2.2. Study Selection Criteria

A two-stage screening process was implemented to identify the most relevant studies. In the first stage, titles and abstracts were screened based on predefined inclusion criteria: (1) original research articles; (2) studies focusing on human breast cancer; (3) investigations of oncogenes as diagnostic, prognostic, or predictive biomarkers; and (4) reports detailing molecular detection methods for oncogenic alterations.

The second stage involved full-text review of potentially eligible articles with more stringent criteria: (1) studies with clearly defined patient cohorts and control groups where applicable; (2) publications providing detailed methodology for oncogene detection; (3) articles reporting clinically relevant outcomes (e.g., diagnostic accuracy, treatment response, survival data); and (4) studies with adequate statistical analysis.

Exclusion criteria were applied to remove: (1) preclinical studies without clinical validation; (2) conference abstracts without full peer-reviewed publication; and (3) duplicate publications reporting overlapping datasets.

2.3. Data Extraction and Quality Assessment

Data extraction was performed using a standardized form capturing: Oncogenes investigated, detection methodologies, key findings (diagnostic accuracy, prognostic value, therapeutic implications), and limitations reported by study authors. Particular attention was paid to potential biases in patient selection, index test interpretation, and reference standard application. Only studies meeting at least moderate quality thresholds were included in the final synthesis.

2.4. Ethical Considerations and Data Synthesis

As a review of previously published data, we prioritized studies that explicitly reported obtaining informed consent and institutional review board approval, particularly for research involving genetic testing or sensitive patient data.

The extracted data were analyzed thematically. Evidence was synthesized to address three key domains: (1) oncogenes with established diagnostic utility in breast cancer; (2) comparison of molecular detection platforms; and (3) clinical applications in risk assessment, early detection, and treatment selection.

2.5. Validation and Peer Review Process

To ensure comprehensiveness, the reference lists of all included studies and relevant review articles were hand-searched for additional publications. The preliminary findings were reviewed by a panel of experts in breast oncology and molecular pathology to validate interpretations and identify any overlooked evidence. Discrepancies in study inclusion or data interpretation were resolved through consensus discussion among all authors.

This rigorous methodology was designed to provide clinicians and researchers with a comprehensive, evidence-based overview of oncogenic biomarkers in breast cancer while transparently acknowledging the limitations inherent in literature reviews, including potential publication bias and the rapid evolution of molecular technologies that may outpace the published literature.

3. RESULTS

The systematic evaluation of the selected literature revealed significant insights into the diagnostic and clinical utility of key oncogenes—HER2, PIK3CA, MYC, BRCA1, and BRCA2—in breast cancer management. Our analysis identified consistent patterns regarding the prevalence of molecular alterations in these oncogenes across different breast cancer subtypes, their detection through various advanced methodologies, and their implications for clinical decision-making. The findings demonstrate that each oncogene presents unique diagnostic challenges and opportunities, with HER2 amplification showing robust predictive value for targeted therapies, PIK3CA mutations serving as potential indicators for PI3K/AKT/mTOR pathway inhibitors, and BRCA1/2 mutations guiding PARP inhibitor therapy selection. Furthermore, the review highlights the evolving role of MYC as both a diagnostic marker and therapeutic target, while also addressing the complexities associated with variant interpretation and the clinical translation of these biomarkers. Collectively, the results underscore the transformative potential of oncogene-based diagnostics in precision oncology while revealing critical gaps in standardization, accessibility, and clinical validation that must be addressed to optimize their implementation in routine practice.

3.1. HER2 (ERBB2)

The human epidermal growth factor receptor 2 (HER2/ERBB2) oncogene plays a pivotal role in the pathogenesis of breast cancer, influencing tumor

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aggressiveness, prognosis, and therapeutic response. HER2 amplification or overexpression occurs in approximately 15–20% of breast cancers and is associated with poor clinical outcomes if left untreated [15]. However, the advent of HER2-targeted therapies, such as trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1), has significantly improved survival rates in HER2-positive breast cancer patients [16]. Given its critical role in diagnosis, prognosis, and treatment selection, HER2 has emerged as one of the most essential biomarkers in breast oncology.

3.1.1. HER2 as a Diagnostic Biomarker

HER2 is a member of the ERBB receptor tyrosine kinase family, which regulates cell proliferation, survival, and differentiation. HER2 gene amplification leads to protein overexpression, resulting in constitutive activation of downstream signaling pathways such as PI3K/AKT and MAPK, promoting uncontrolled cell growth and tumorigenesis [17]. The clinical significance of HER2 as a diagnostic biomarker stems from its strong association with aggressive tumor behavior, including high histological grade, increased proliferation rates, and poor prognosis [18].

Immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) remain the gold standard methods for HER2 testing, as endorsed by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) [19]. IHC evaluates HER2 protein expression, scored on a scale of 0 to 3+, where scores of 3+ indicate HER2 positivity, 0 or 1+ denote negativity, and 2+ cases require further FISH testing for gene amplification confirmation [20]. FISH directly assesses HER2 gene copy number, with a HER2/CEP17 ratio ≥2.0 or an average HER2 copy number ≥6.0 signals/cell considered positive [21].

Despite their widespread use, IHC and FISH have limitations, including interobserver variability and tissue heterogeneity [22]. Emerging techniques such as chromogenic in situ hybridization (CISH), silver in situ hybridization (SISH), and digital pathology are being explored to enhance accuracy and reproducibility [23]. Additionally, next-generation sequencing (NGS) and droplet digital PCR (ddPCR) are gaining traction for detecting HER2 amplification in circulating tumor DNA (ctDNA), offering a non-invasive alternative for monitoring disease progression and treatment resistance [24].

3.1.2. Molecular Detection of HER2: Advances and Challenges

The molecular characterization of HER2 has expanded beyond traditional IHC and FISH, incorporating novel genomic and transcriptomic approaches. RNA-based assays, such as NanoString and quantitative reverse transcription PCR (qRT-PCR), enable quantification of HER2 mRNA levels, providing complementary data to protein-based methods [2]. Whole-exome sequencing (WES) and whole-genome sequencing (WGS) have identified rare HER2 mutations (e.g., L755S, V777L) that may confer resistance to HER2-targeted therapies, highlighting the need for comprehensive molecular profiling [10].

Liquid biopsy approaches, particularly ctDNA analysis, are revolutionizing HER2 detection by enabling real-time monitoring of tumor dynamics. Studies have demonstrated that HER2 amplification in ctDNA correlates with treatment response and progression-free survival, offering a minimally invasive tool for disease surveillance [25]. However, challenges remain in standardizing ctDNA assays, as sensitivity varies depending on tumor burden and assay methodology [26].

Another promising advancement is the use of artificial intelligence (AI) in HER2 interpretation. AI-powered image analysis can reduce subjectivity in IHC scoring, improving diagnostic consistency [27]. Furthermore, multi-omics integration—combining genomic, transcriptomic, and proteomic data—holds potential for refining HER2 classification and identifying novel therapeutic targets [28].

3.1.3. Clinical Utility of HER2 in Breast Cancer Management

HER2 status is not only a diagnostic marker but also a critical determinant of therapy selection. HER2-positive breast cancers are highly responsive to targeted therapies, which have transformed the treatment landscape. Trastuzumab, a monoclonal antibody against HER2, was the first targeted agent to demonstrate significant survival benefits in both early and metastatic settings [29]. The addition of pertuzumab, which inhibits HER2 dimerization, further improves outcomes, particularly in neoadjuvant and metastatic regimens [30].

For patients with residual disease after neoadjuvant therapy, T-DM1—an antibody-drug conjugate—has shown superior efficacy compared to trastuzumab alone, reducing recurrence risk [31]. Novel agents such as trastuzumab deruxtecan (T-DXd), a HER2-directed antibody-drug conjugate with a topoisomerase I inhibitor payload, have demonstrated remarkable activity even in HER2-low breast cancers, expanding the therapeutic paradigm [32].

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Despite these advances, resistance to HER2-targeted therapies remains a challenge. Mechanisms include activation of alternative signaling pathways (e.g., PI3K/mTOR), HER2 mutations, and immune evasion [33]. Ongoing research focuses on combination strategies, such as HER2 inhibitors with CDK4/6 inhibitors or immune checkpoint inhibitors, to overcome resistance [34].

HER2-low breast cancer (IHC 1+ or 2+ without gene amplification) represents a newly defined subset, accounting for up to 50% of cases. Recent trials have shown that T-DXd improves outcomes in HER2-low metastatic disease, prompting a reevaluation of HER2 testing criteria and therapeutic approaches [35].

3.2. MYC

The MYC oncogene is a well-characterized driver of tumorigenesis in various cancers, including breast cancer, where its amplification and overexpression are associated with aggressive disease phenotypes, poor prognosis, and resistance to therapy [36]. MYC encodes a transcription factor that regulates numerous cellular processes, including proliferation, apoptosis, metabolism, and differentiation, making it a critical player in cancer progression [37]. In breast cancer, MYC amplification occurs in approximately 15–30% of cases, with higher frequencies observed in triple-negative and HER2-positive subtypes [38]. Given its pivotal role in tumor biology, MYC has been extensively investigated as a potential diagnostic biomarker, with emerging utility in molecular detection methods and clinical decision-making [39].

3.2.1. MYC as a Diagnostic Biomarker in Breast Cancer

The diagnostic potential of MYC in breast cancer stems from its frequent genetic alterations and correlation with disease aggressiveness. Fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC) have been widely used to detect MYC amplification and protein overexpression, respectively [40]. Studies have shown that MYC amplification is associated with high histological grade, larger tumor size, and lymph node metastasis, reinforcing its prognostic significance [41]. Additionally, MYC overexpression has been linked to the basal-like subtype of breast cancer, which is typically associated with poor clinical outcomes [2].

Circulating tumor DNA (ctDNA) analysis has further expanded the diagnostic applications of MYC by enabling non-invasive detection of MYC amplification in metastatic breast cancer patients [10]. Liquid biopsy approaches have demonstrated that MYC copy number variations (CNVs) in ctDNA correlate with tumor burden and treatment response, offering a dynamic monitoring tool [42]. Moreover, MYC-driven gene expression signatures have been incorporated into multi-gene assays, such as the PAM50 classifier, to improve breast cancer subtyping and risk stratification [43].

3.2.2. Molecular Detection of MYC Alterations

Advancements in molecular techniques have enhanced the precision of MYC detection in breast cancer. Next-generation sequencing (NGS) has enabled comprehensive profiling of MYC alterations, including point mutations, amplifications, and translocations [44]. Whole-genome sequencing (WGS) studies have identified MYC as a common site of structural variations, particularly in hormone receptor-negative breast cancers [45]. Digital droplet PCR (ddPCR) has also emerged as a sensitive method for quantifying MYC amplification in both tissue and liquid biopsies, with high concordance to FISH results [46].

Single-cell RNA sequencing (scRNA-seq) has provided insights into MYC's heterogeneous expression within tumors, revealing subpopulations of MYC-high cells that may drive therapy resistance [47]. Furthermore, CRISPR-based screening has identified synthetic lethal interactions with MYC-amplified breast cancers, highlighting potential therapeutic vulnerabilities [48]. These molecular approaches not only improve diagnostic accuracy but also facilitate the identification of novel therapeutic targets.

3.2.3. Clinical Utility of MYC in Breast Cancer Management

The clinical implications of MYC in breast cancer extend beyond diagnosis, influencing therapeutic strategies and patient outcomes. Preclinical studies have demonstrated that MYC overexpression confers resistance to endocrine therapy in estrogen receptor (ER)-positive breast cancer, suggesting that MYC status could guide treatment selection [49]. In HER2-positive breast cancer, MYC amplification has been associated with trastuzumab resistance, prompting investigations into MYC-targeted combination therapies [50].

Several MYC-targeting approaches are under investigation, including small-molecule inhibitors, RNA interference (RNAi), and epigenetic modulators [51]. Notably, bromodomain and extraterminal (BET) inhibitors, which disrupt MYC transcription, have shown promise in preclinical models of MYC-driven breast cancer [52]. Additionally, synthetic lethality strategies, such as

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combining MYC inhibition with PARP inhibitors, are being explored to exploit MYC-associated DNA repair deficiencies [53].

Despite these advances, targeting MYC remains challenging due to its pervasive role in normal cellular functions and the lack of a druggable binding pocket [54]. Alternative strategies, such as indirect MYC suppression through upstream regulators or downstream effectors, are being pursued to circumvent these limitations [55]. Clinical trials evaluating MYC-directed therapies are ongoing, with early-phase studies reporting variable responses, underscoring the need for biomarker-driven patient selection [56].

3.2.4. Challenges and Future Directions

While MYC holds significant promise as a diagnostic and therapeutic biomarker, several challenges must be addressed for its successful clinical translation. Tumor heterogeneity and temporal evolution of MYC amplification pose difficulties in consistent detection, necessitating repeated molecular profiling in advanced disease [57]. Additionally, standardized thresholds for MYC amplification and overexpression are lacking, leading to variability across studies and diagnostic platforms [58].

Future research should focus on integrating multi-omics data to refine MYC's predictive value and identify co-alterations that modulate its oncogenic effects [28]. Longitudinal studies tracking MYC dynamics during treatment will be crucial to understanding its role in acquired resistance [59]. Furthermore, the development of more specific MYC inhibitors and companion diagnostics will be essential to realizing its full clinical potential [60].

3.3. PIK3CA

The PIK3CA gene encodes the p110α catalytic subunit of phosphatidylinositol 3-kinase (PI3K), a key regulator of the PI3K/AKT/mTOR signaling pathway, which governs cellular proliferation, survival, and metabolism [61]. Given its frequent mutation in breast cancer (30–40% of cases), PIK3CA has garnered substantial attention as a potential diagnostic biomarker, with implications for early detection, therapeutic targeting, and resistance mechanisms [62].

3.3.1. PIK3CA Mutations as a Diagnostic Biomarker

The diagnostic potential of PIK3CA mutations stems from their high prevalence and association with specific breast cancer subtypes. The most common mutations occur in exons 9 and 20, particularly at hotspots E542K, E545K, and H1047R, leading to constitutive PI3K pathway activation [63]. These mutations are predominantly found in estrogen receptor-positive (ER+) and HER2-negative tumors, suggesting a role in endocrine therapy resistance [64]. Studies have demonstrated that PIK3CA-mutated tumors exhibit distinct clinicopathological features, including lower histological grade and reduced metastatic potential compared to PIK3CA wild-type tumors, yet paradoxically, they may confer resistance to standard therapies [65].

Liquid biopsy approaches, such as circulating tumor DNA (ctDNA) analysis, have enabled non-invasive detection of PIK3CA mutations, offering a promising tool for early diagnosis and monitoring [24]. The U.S. Food and Drug Administration (FDA) has approved the PIK3CA mutation test (therascreen® PIK3CA RGQ PCR Kit) as a companion diagnostic for alpelisib, a PI3Kα inhibitor, in combination with fulvestrant for advanced HR+/HER2- breast cancer [8]. This underscores the clinical relevance of PIK3CA as a biomarker in guiding treatment decisions.

3.3.2. Molecular Detection Techniques for PIK3CA Mutations

Accurate detection of PIK3CA mutations is critical for patient stratification and personalized therapy. Several molecular techniques are employed, each with distinct advantages and limitations:

A. Next-Generation Sequencing (NGS): NGS offers high sensitivity and the ability to detect multiple mutations simultaneously, making it ideal for comprehensive genomic profiling [66]. Targeted NGS panels, such as those focusing on cancer-related genes, are increasingly used in clinical settings to identify PIK3CA alterations alongside other oncogenic drivers [67].
B. Digital Droplet PCR (ddPCR): ddPCR provides ultra-sensitive quantification of mutant alleles, even at low frequencies (<1%), making it suitable for ctDNA analysis in liquid biopsies [68]. Its high precision is particularly valuable for monitoring minimal residual disease (MRD) and detecting emerging resistance mutations [69].
C. Sanger Sequencing: While less sensitive than NGS or ddPCR, Sanger sequencing remains a gold standard for validating mutations detected by other methods due to its high specificity [70]. However, its limited sensitivity (~15–20% mutant allele frequency)

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restricts its utility in heterogeneous tumor samples [71].

D. Pyrosequencing and ARMS-PCR: These methods offer rapid and cost-effective mutation screening, with pyrosequencing providing quantitative allele frequency data and amplification-refractory mutation system PCR (ARMS-PCR) enabling specific detection of known hotspot mutations [72].

Despite technological advancements, challenges persist in mutation detection, including tumor heterogeneity, low DNA yield from biopsies, and the need for standardized testing protocols across laboratories [73].

3.3.3. Clinical Utility of PIK3CA Mutations in Breast Cancer Management

The therapeutic implications of PIK3CA mutations have been extensively investigated, particularly in the context of PI3K/AKT/mTOR pathway inhibitors. The SOLAR-1 trial demonstrated that alpelisib, a selective PI3Kα inhibitor, significantly improved progression-free survival (PFS) in patients with PIK3CA-mutated advanced HR+/HER2- breast cancer when combined with fulvestrant [74]. This led to the FDA approval of alpelisib in 2019, marking a milestone in precision oncology for this patient subset [75].

However, resistance to PI3K inhibitors remains a challenge, often arising through compensatory mechanisms such as mTOR activation or loss of PTEN function [76]. Combination therapies targeting both PI3K and downstream effectors (e.g., mTOR inhibitors like everolimus) are under investigation to overcome resistance [77]. Additionally, emerging evidence suggests that PIK3CA mutations may influence response to CDK4/6 inhibitors, with some studies indicating enhanced efficacy in PIK3CA-mutated tumors, though further validation is required [78].

Beyond treatment selection, PIK3CA mutations have prognostic implications. While some studies associate these mutations with favorable outcomes due to less aggressive tumor biology, others highlight their role in therapy resistance, underscoring the need for context-specific interpretation [79].

3.3.4. Future Perspectives and Challenges

Despite progress, several challenges hinder the widespread implementation of PIK3CA testing in routine clinical practice. Tumor heterogeneity and clonal evolution necessitate longitudinal monitoring via liquid biopsies to capture dynamic mutational changes [10]. Additionally, the cost and accessibility of advanced molecular techniques remain barriers in low-resource settings [80]. Future research should focus on:

- Developing more potent and selective PI3K inhibitors with improved safety profiles.
- Identifying predictive biomarkers for PI3K inhibitor response beyond PIK3CA mutations.
- Integrating multi-omics approaches (e.g., transcriptomics, proteomics) to refine patient stratification [81].

3.4. BRCA1 and BRCA2

These tumor suppressor genes play a crucial role in DNA repair through homologous recombination, and their dysfunction leads to genomic instability and increased cancer susceptibility [82]. The identification of BRCA1/2 mutations has revolutionized breast cancer diagnostics, risk assessment, and therapeutic decision-making, positioning these genes as essential biomarkers in clinical oncology [83].

3.4.1. BRCA1 and BRCA2 as Diagnostic Biomarkers

The association between BRCA1/2 mutations and hereditary breast and ovarian cancer (HBOC) syndrome was first established in the 1990s, with subsequent studies confirming their high penetrance [84]. Women carrying pathogenic BRCA1 mutations have a 55–65% lifetime risk of developing breast cancer, while BRCA2 mutation carriers face a 45% risk, significantly higher than the general population's 12% risk [85]. These mutations are inherited in an autosomal dominant pattern, necessitating genetic testing in high-risk individuals [86].

BRCA1-associated breast cancers are typically triple-negative (estrogen receptor [ER]-, progesterone receptor [PR]-, HER2-), aggressive, and occur at a younger age, whereas BRCA2-related tumors are more often hormone receptor-positive [87]. This distinction has diagnostic implications, as BRCA1 mutations may necessitate different screening protocols compared to BRCA2 or sporadic cases [88]. Furthermore, BRCA1/2 testing is now integral to identifying high-risk families, enabling early surveillance and prophylactic interventions [89].

3.4.2. Molecular Detection of BRCA1/2 Mutations

Accurate detection of BRCA1/2 mutations is critical for clinical decision-making. Several molecular techniques are employed, each with advantages and limitations.

A. Sanger Sequencing:

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Traditionally, Sanger sequencing was the gold standard for BRCA1/2 mutation detection, offering high accuracy for small-scale analyses [90]. However, its labor-intensive nature and inability to detect large genomic rearrangements limit its utility in high-throughput settings [91].

B. Next-Generation Sequencing (NGS):

NGS has largely replaced Sanger sequencing due to its ability to simultaneously analyze multiple genes with high sensitivity and reduced cost [92]. Multiplex panels now include BRCA1/2 alongside other breast cancer-related genes (e.g., PALB2, TP53, CHEK2), improving diagnostic yield [93]. NGS also detects copy number variations (CNVs), which account for ~10% of BRCA1/2 mutations [94].

C. Multiplex Ligation-Dependent Probe Amplification (MLPA)

MLPA is specifically designed to identify large deletions and duplications in BRCA1/2, which are missed by conventional sequencing [95]. It is often used as a complementary test following NGS to ensure comprehensive mutation profiling [96].

D. Polymerase Chain Reaction (PCR)-Based Methods

Allele-specific PCR and quantitative PCR (qPCR) are rapid, cost-effective techniques for screening known founder mutations (e.g., BRCA1 c.68_69delAG in Ashkenazi Jews) [97]. However, their utility is restricted to populations with well-characterized mutation hotspots [98].

E. Emerging Technologies

Third-generation sequencing (e.g., Oxford Nanopore, PacBio) and digital droplet PCR (ddPCR) are being explored for their potential to improve mutation detection sensitivity and turnaround time [99]. Additionally, artificial intelligence (AI)-based algorithms are being integrated into variant interpretation to classify mutations of uncertain significance (VUS) more accurately [100].

3.4.3. Clinical Utility of BRCA1/2 Testing

The clinical applications of BRCA1/2 testing extend beyond diagnosis, influencing risk management, treatment selection, and familial counseling.

A. Risk Assessment and Prophylactic Measures

BRCA1/2 mutation carriers are offered enhanced surveillance, including annual mammography, breast MRI, and transvaginal ultrasound for ovarian cancer screening [101]. Risk-reducing strategies such as prophylactic mastectomy and salpingo-oophorectomy significantly decrease cancer incidence and mortality [102]. A meta-analysis demonstrated that bilateral mastectomy reduces breast cancer risk by 90–95% in BRCA1/2 carriers [103].

B. Therapeutic Implications

BRCA1/2-deficient tumors exhibit synthetic lethality with poly (ADP-ribose) polymerase (PARP) inhibitors, which exploit defective homologous recombination repair [104]. Olaparib, talazoparib, and rucaparib are FDA-approved for BRCA-mutated metastatic breast cancer, improving progression-free survival [105]. Additionally, platinum-based chemotherapies show enhanced efficacy in BRCA1/2-associated cancers due to their DNA-damaging mechanism [106].

C. Familial Genetic Counseling

Identifying a pathogenic BRCA1/2 mutation has profound implications for family members, as first-degree relatives have a 50% chance of inheriting the mutation [107]. Cascade testing ensures early detection and intervention in at-risk relatives, reducing overall cancer burden [108]. Ethical considerations, including psychological impact and insurance discrimination, must be addressed during counseling [109].

D. Prognostic Value

While BRCA1 mutations are associated with poorer outcomes due to aggressive tumor biology, BRCA2 carriers often have survival rates comparable to sporadic cases when detected early [110]. However, conflicting data exist, necessitating further research on long-term prognostic stratification [111].

3.4.4. Challenges and Future Directions

Despite advancements, BRCA1/2 testing faces challenges, including:

A. Variant Interpretation: Up to 20% of BRCA1/2 test results report VUS, complicating clinical management [112].
B. Access and Cost Disparities: Genetic testing remains inaccessible in low-resource regions, exacerbating healthcare inequities [113].
C. Psychosocial Impact: Positive results may cause anxiety, while false negatives provide false reassurance [114].

Future research should focus on:

A. Expanding multi-gene panels to include emerging breast cancer susceptibility genes [115].
B. Developing functional assays to clarify VUS pathogenicity [116].
C. Integrating liquid biopsies for non-invasive BRCA1/2 mutation detection [117].

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4. DISCUSSION

Although lifestyle factors contribute to the onset of breast cancer [118], oncogenes play pivotal roles in breast cancer pathogenesis, influencing tumor progression, treatment response, and patient outcomes. The molecular detection of these oncogenes has significantly enhanced the precision of breast cancer diagnostics, enabling tailored therapeutic strategies and improving clinical decision-making [3]. While analogous research has been performed on various cancer types [119], it was essential to undertake this review specifically concerning breast cancer.

HER2 (ERBB2) amplification and overexpression occur in approximately 15-20% of breast cancers and are associated with aggressive tumor behavior and poor prognosis [15]. The introduction of HER2-targeted therapies, such as trastuzumab and pertuzumab, has revolutionized treatment for HER2-positive breast cancer, underscoring the clinical utility of HER2 as a diagnostic and predictive biomarker [120]. Immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) remain the gold standard for HER2 detection, though next-generation sequencing (NGS) and digital PCR are emerging as more sensitive alternatives [19]. However, challenges persist in HER2 testing, including intratumoral heterogeneity and discordance between primary and metastatic lesions, necessitating standardized protocols to ensure accuracy [121].

PIK3CA, encoding the catalytic subunit of PI3K, is mutated in up to 40% of hormone receptor-positive (HR+) breast cancers, leading to constitutive activation of the PI3K/AKT/mTOR pathway and resistance to endocrine therapy [122]. PIK3CA mutations are detectable via PCR-based assays and NGS, with emerging evidence supporting their role as predictive biomarkers for PI3K inhibitors such as alpelisib [8]. Despite this, the clinical utility of PIK3CA testing remains debated due to the variable response to targeted therapies and the influence of coexisting genetic alterations [62]. Further research is needed to elucidate the optimal use of PIK3CA mutations in guiding treatment decisions.

The MYC oncogene is amplified in 15-30% of breast cancers and is associated with high proliferation rates, therapy resistance, and poor survival [38]. MYC overexpression promotes genomic instability and metabolic reprogramming, making it a potential therapeutic target [36]. However, direct targeting of MYC has proven challenging due to its unstructured protein nature, necessitating alternative strategies such as MYC pathway inhibition or synthetic lethality approaches [51]. Liquid biopsy-based detection of MYC amplification is an area of active investigation, offering a non-invasive method for monitoring disease progression and treatment response [10].

Germline mutations in BRCA1 and BRCA2 are well-established risk factors for hereditary breast cancer, with BRCA1 mutations linked to triple-negative breast cancer (TNBC) and BRCA2 mutations more commonly associated with HR+ tumors [84]. PARP inhibitors (e.g., olaparib, talazoparib) have demonstrated significant efficacy in BRCA-mutated breast cancers, highlighting the importance of genetic testing for BRCA status [105]. Multigene panel testing, including BRCA1/2, is now standard in high-risk patients, though challenges such as variants of uncertain significance (VUS) and ethical considerations regarding incidental findings remain [83].

The integration of these oncogenic biomarkers into clinical practice has transformed breast cancer management, facilitating early detection, risk stratification, and personalized therapy. However, several challenges must be addressed, including assay standardization, tumor heterogeneity, and the need for robust biomarkers predictive of treatment response. Future research should focus on multi-omics approaches, combining genomic, transcriptomic, and proteomic data to refine biomarker utility and develop novel therapeutic targets.

5. CONCLUSION

The identification and molecular characterization of oncogenes such as HER2, PIK3CA, MYC, and BRCA1/2 have significantly advanced breast cancer diagnostics and therapeutics. These biomarkers provide critical insights into tumor biology, enabling precision medicine approaches that improve patient outcomes. HER2-targeted therapies and PARP inhibitors for BRCA-mutated cancers exemplify the successful translation of molecular discoveries into clinical practice.

Despite these advancements, challenges remain in optimizing detection methods, resolving tumor heterogeneity, and validating predictive biomarkers for emerging therapies. The continued evolution of high-throughput sequencing, liquid biopsy technologies, and artificial intelligence-driven data analysis holds promise for further refining biomarker utility in breast cancer.

In summary, the integration of oncogenic biomarkers into routine clinical practice represents a paradigm shift in breast cancer care, emphasizing early detection, personalized treatment, and improved survival. Future efforts should prioritize large-scale validation studies, cost-effective testing strategies, and global accessibility to ensure equitable implementation of these advancements.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Ethical statement

This article is a literature review and does not involve any studies with human participants or animals performed by any of the authors. Therefore, ethical approval was not required.

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