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# Synthesizing The Evidence: TP53 Mutations as a Prognostic and Predictive Biomarker in Breast Cancer

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***ABSTRACT***

*The journey to personalize breast cancer therapy increasingly navigates the complex landscape of somatic TP53 mutations, the most frequent genetic drivers of this disease. Moving beyond a simple prognostic badge, we now understand these mutations create a spectrum of clinical behaviors, deeply influenced by their specific functional impact and, critically, by their genetic companions. A systematic literature review was conducted across three major electronic databases: ScienceDirect, ProQuest, and Scopus. The search was restricted to peer-reviewed journal articles published in English between 2021 and 2024 to ensure the inclusion of recent evidence. The confluence of TP53 and PIK3CA mutations stands out as a devastating synergy that heralds a tumor phenotype with profound resistance to common chemotherapy regimens, especially taxanes, and the direst survival outcomes. This genetic context also subtly reshapes responses to HER2-targeted drugs, revealing that TP53's influence is both powerful and context-dependent. A more nuanced profiling, one that accounts for these critical genetic interactions, is no longer a future aspiration but a present necessity. These findings collectively advocate for the integration of comprehensive molecular profiling, including nuanced TP53 and PIK3CA assessment, into clinical decision-making.*

## 1. INTRODUCTION

Breast cancer (BC) constitutes a clinically distinct entity characterized by heterogeneous biological subtypes exhibiting unique molecular profiles and differential therapeutic responsiveness. In hereditary contexts, germline mutations in the TP53 tumor suppressor gene drive mammary carcinogenesis and tumor progression by disrupting genomic integrity. Hereditary breast cancer pathogenesis arises from deleterious mutations in genes governing critical cellular processes, including proliferation regulation, Deoxyribonucleic Acid (DNA) damage repair, and tumor suppression. Such mutations confer elevated lifetime risks for breast malignancies. Predominant high-penetrance susceptibility genes implicated in hereditary breast cancer syndromes include TP53, PTEN, CDH1, STK11, and NF1 (Sokolova et al., 2023; Testa et al., 2020; World Health Organization, 2025)

In the era of precision oncology, p53 is the most frequently mutated gene in breast cancer, which represents a promising personalized strategy. The p53 protein orchestrates a sophisticated defense network, coordinating cell cycle arrest, DNA repair, and programmed cell death in response to cellular stress (Moulder et al., 2018). However, somatic TP53 mutations subvert these tumor-suppressive functions, often conferring more aggressive disease phenotypes and fostering resistance to conventional DNA-damaging therapies. The clinical implications of these mutations are further complicated by their functional heterogeneity, as not all mutations are equivalent, with specific variants and their co-occurrence with other genetic lesions, such as PIK3CA mutations, creating distinct prognostic and predictive profiles (Hwang et al., 2024; Monge et al., 2025; Wang et al., 2023). Notably, p53-mediated transcriptional programs serve as the central determinant of cellular fate following therapeutic stress, whether instigated by DNA-damaging modalities or taxane-induced mitotic catastrophe(Shahbandi et al., 2020).

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Prognostic biomarkers are clinical or biological characteristics that provide information about a patient's likely health outcome (e.g., disease recurrence, progression-free survival, and overall survival), regardless of treatment. These biomarkers are measured before treatment and identify tumor-specific molecular or histopathological characteristics associated with long-term outcome or disease progression, independent of treatment (Nalejska et al., 2014). To determine how TP53 mutations affect BC immunogenicity, the previous study compared the expression differences of immune-related and stroma-related genes between the TP53 mutant and TP53-wildtype (wt) groups. The results showed that in the mutation group, the ImmuneScore and StromalScore levels were both significantly increased. In addition, the expression of several HLA gene families was increased dramatically in the mutation group. These results revealed that TP53 mutation is an independent predictive factor for overall survival (OS) in breast cancer patients (Zhang et al., 2021). Furthermore, to develop a clinical quantitative tool for predicting OS in breast cancer patients, a nomogram was constructed based on the results of multivariable Cox regression. In this nomogram, significant variables, including TP53 mutation, age, stage, and TNM status, were used to assign points (S. Huang et al., 2024; Jiang et al., 2021; Yu et al., 2024).

Several studies have consistently demonstrated the predictive significance of TP53 in several stages of malignancy. In the early stages of malignancy, such as stages I and II, studies have shown that TP53 mutations or overexpression can serve as predictive markers for the aggressiveness of certain diseases and a poor prognosis (Felipe-Silva et al., 2016). Higher Tp53 expression levels or the presence of p53 mutations in these stages are often associated with increased tumor invasiveness, higher rates of metastasis, and reduced overall survival rates for patients (Graur et al., 2016). In a study conducted by Rahadiani et al., patients diagnosed with stage IB, II, and IIIA hepatocellular carcinoma (HCC) were included. The study revealed that the expression of Tp53 was highest in individuals with stage II HCC, followed by those with stage IB and stage IIIA (Rahadiani et al., 2023). This finding contrasts with another study that demonstrated a positive correlation between Tp53 expression and tumor staging, where patients with stage III-IV HCC exhibited a 90.9% rate of positive Tp53 expression. By examining their influence on prognosis, therapy response, and the emerging potential for targeted intervention, we aim to delineate their integral place in the evolving paradigm of personalized cancer medicine. This review synthesizes contemporary evidence to critically appraise the role of TP53 mutations as dynamic biomarkers in breast cancer (Arab et al. 2025).

## 2. METHOD

A systematic literature search was conducted across three major electronic databases: ScienceDirect, ProQuest, and Scopus. The search strategy employed the following key terms and Boolean operators: "breast cancer" AND "targeting p53" AND "personalized medicine" AND "targeted therapy". The search was restricted to peer-reviewed journal articles published in English between 2021 and 2024 to ensure the inclusion of recent evidence.

The initial database queries yielded a total of 89 publications: 5 from ScienceDirect, 54 from ProQuest, and 30 from Scopus. The selection process involved a two-stage screening. First, the titles and abstracts of all retrieved articles were reviewed for relevance to the core themes of p53 biology, targeted therapy, and personalized medicine in breast cancer, resulting in 18 potentially eligible articles. Subsequently, a full-text assessment of these 18 articles was performed. The final inclusion was contingent upon the study being a primary research article, which led to the exclusion of review articles, editorials, and conference abstracts.

## 3. RESULT AND DISCUSSION

### Result

Seven publications that satisfied the selection criteria were identified for qualitative synthesis, as summarized in Table 3.1. The methodological approaches were dominated by retrospective cohort studies (A1, A3, A4, A5, A7, A8), which facilitated detailed and extensive analysis. The complementary evidence consisted of a single case-control (A2) and a cross-sectional study (A6). The integrity of the data was consistently upheld across all studies through

clearly documented data sources and the application of validated tools, lending substantial support to the overall reliability of the conclusions drawn.

Table 1. Summary of findings on TP53 Mutations as a Prognostic and Predictive Biomarker Breast Cancer

| Study | Author Year | Title | Outcomes measured | Key Findings |
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| A1 | Zhao et al., 2021 | The effect of PIK3CA and TP53 on prognosis in patients with Triple-negative breast cancer (TNBC): a single institution's long-term follow-up (6 years) | A longitudinal study investigating prognostic markers in breast cancer revealed several critical insights. The analysis identified lymph node metastasis as the most significant factor influencing patient prognosis. Molecularly, a striking enrichment of both PIK3CA and TP53 mutations was observed in patients with triple-negative breast cancer (TNBC) compared to other subtypes. | The concurrent presence of PIK3CA and TP53 mutations emerged as a powerful harbinger of poor outcomes, strongly associated with reduced progression-free survival. The study also highlighted geographic disparities in overall survival. These results underscore the utility of these genetic alterations as biomarkers for unfavorable prognosis in TNBC, while also pointing to underlying socio-economic determinants of patient survival. |
| A2 | Andrikopoulou et al., 2021 | TP53 mutations determined by targeted NGS in breast cancer: a case-control study | The study cohort comprised 82 female patients diagnosed with Stage I–III breast cancer. To investigate somatic TP53 mutations, the researchers utilized next-generation sequencing (NGS) on matched formalin-fixed paraffin-embedded (FFPE) tumor blocks and peripheral blood samples. | TP53-mutated cases surviving without recurrence for a median of 16.3 months, compared to 62.9 months in others. This aggressive disease course was linked to specific genetic alterations, predominantly the TP53 p.(Cys275Tyr) mutation, which was often accompanied by a concurrent PIK3CA mutation in a subset of tumors. |
| A3 | Mitri et al., 2022 | Impact of TP53 mutations in Triple Negative Breast Cancer | This retrospective analysis of 96 TNBC patients evaluated the prognostic role of TP53 mutations by integrating RNA sequencing data with a novel functional metric, the Evolutionary Action (EAp53) score. A data-driven approach was employed to stratify patients with missense mutations into "low-impact" (EAp53 1-69) and "high-impact" (EAp53 70-99) groups, and the associations between these TP53 status categories and survival outcomes. | This study revealed that the prognostic impact of TP53 mutations in triple-negative breast cancer (TNBC) is not uniform but is critically dependent on the mutation's functional impact and location. While the simple presence of a TP53 mutation showed a non-significant trend towards worse outcomes, a nuanced analysis using the Evolutionary Action score (EAp53) identified a small subset of patients with low-impact missense mutations (EAp53 1-69) who faced significantly poorer recurrence-free and overall survival, and a startling 0% pathological complete response rate to neoadjuvant |

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| | | | | chemotherapy. |
| A4 | Liu et al., 2022 | Molecular landscape of TP53 mutations in breast cancer and their utility for predicting the response to HER-targeted therapy in HER2 amplification-positive and HER2 mutation-positive amplification-negative patients | After an initial analysis in a large cohort, the study specifically interrogated how TP53 status influences the efficacy of HER2-targeted therapies. This involved assessing its role in antibody-based treatment using the MSK-BREAST cohort and, more importantly, its impact on TKI response by analyzing ctDNA from patients enrolled in pyrotinib trials. The clinical relevance of these findings was solidified through extensive external validation across multiple independent datasets. | The study first confirmed its role as a marker of aggressive biology and resistance to standard anti-HER2 antibody therapy. However, it also revealed a more nuanced narrative for targeted agents. The presence of a TP53 mutation did not influence TKI efficacy in canonical HER2-positive breast cancer. Instead, its negative predictive power was uniquely relevant for the emerging subset of HER2-mutant patients, suggesting that genotyping for both HER2 and TP53 could be vital for optimizing TKI treatment strategies in this specific population. |
| A5 | Choi et al., 2023 | Prognostic significance of TP53 and PIK3CA mutations analyzed by next-generation sequencing in breast cancer | This study employed next-generation sequencing (NGS) to map the landscape of somatic mutations in a surgical cohort of 265 patients with invasive ductal carcinoma of the breast and to evaluate their prognostic significance. Using a targeted panel for 143 cancer-related genes, the investigation quantified the prevalence of somatic mutations and assessed their association with clinical outcomes over a median follow-up of 48 months. | PIK3CA mutations (the most prevalent at 44%) were associated with a more favorable disease-free survival, TP53 mutations (the second most frequent) were significantly correlated with poorer outcomes. This study underscores that specific somatic mutational profiles, readily identifiable through NGS, hold substantial potential as biomarkers for prognostic stratification in breast cancer. |
| A6 | X. Y. Lin et al., 2023 | Concomitant PIK3CA and TP53 mutations in breast cancer: an analysis of clinicopathologic and mutational features, neoadjuvant therapeutic response, and prognosis | This retrospective analysis defined its outcomes through a dual approach. First, it assessed the relationship between PIK3CA/TP53 co-mutations and a spectrum of variables encompassing clinicopathological traits, comprehensive mutational profiles, and pathological responses to neoadjuvant therapy. Second, to ascertain prognostic validity, the study leveraged the METABRIC dataset to determine the association between this specific genetic signature and overall survival. | The study identified a synergistic deleterious effect between PIK3CA and TP53 mutation. Co-mutated tumors were overwhelmingly aggressive, showing a strong association with poor-prognosis clinical features. Therapeutically, they conferred significant resistance to neoadjuvant treatment than taxanes. This genetic combination translated to a tangible clinical detriment, as confirmed by its robust association with poorer overall survival in a large |

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| | | | | external dataset. |
| A7 | Huang et al., 2024 | TP53-specific mutations serve as a potential biomarker for homologous recombination deficiency in breast cancer: a clinical next-generation sequencing study | Genomic analysis was conducted on 119 breast cancer patients (the BRCA-119 cohort) using a targeted 520-gene NGS panel on both tumor and matched normal DNA. The key molecular parameters extracted from the sequencing data included somatic mutations, tumor mutation burden (TMB), and genomic HRD scores. For external validation, these assessments were replicated in a separate cohort of 47 patients. | The predictive utility of mutations was found to be highly variable. However, by subclassifying them based on their HRD association, the researchers developed a refined model. A composite signature of "HRD-high" and "HRD-common" TP53 mutations proved to be a powerful classifier (AUC=0.80), demonstrating that profiling specific mutation characteristics significantly improves the assessment of genomic instability. |
| A8 | Hwang et al., 2024 | Clinical relevance of TP53 mutation and its characteristic in breast cancer with long-term follow-up date | The study assessed the association between TP53 mutational status and oncologic outcomes in breast cancer patients. The primary outcomes measured included survival differences, analyzed through stratified log-rank tests and Cox regression models. These comparisons were stratified not only by the presence of a TP53 mutation but also by specific mutation characteristics, such as type and genomic location. Mutations within exons 5-9 were detected via polymerase chain reaction–denaturing high-performance liquid chromatography (PCR-DHPLC) followed by direct sequencing. | In an investigation of 650 individuals, TP53 mutations were identified in approximately one-quarter of the breast cancer cohort. The presence of any TP53 mutation was conclusively associated with a more aggressive disease course, substantially increasing the risk of recurrence and mortality over 10 years. However, a nuanced finding emerged upon closer examination: when analyzing only the patients with TP53 mutations, the specific molecular characteristics, such as whether it was a missense hotspot mutation or its location within the gene—did not confer additional prognostic stratification. This suggests that the simple dichotomization of TP53 status (mutated vs. wild-type) is a powerful prognostic tool, overshadowing the subtleties of the mutation's nature. |

## Discussion

A central challenge in the management of breast cancer lies in predicting and overcoming therapeutic resistance, particularly in aggressive subtypes. The findings consolidated in this review position somatic TP53 mutations at the heart of this challenge. Far from being a monolithic biomarker, the TP53 mutational landscape delineates a spectrum of clinical behaviors, where the confluence of specific mutation characteristics and co-mutational partners, such as PIK3CA, creates a phenotype of marked chemoresistance and poor survival. Understanding these genetic hierarchies is thus paramount for developing effective strategies for high-risk patient populations.

Central to its tumor-suppressive role, stress-activated p53 eliminates genetically compromised cells by transcriptionally inducing genes that promote apoptosis and cell-cycle arrest. This canonical pathway prevents aberrant cell proliferation and constitutes the most extensively characterized function of p53 (Hertel & Storchová, 2025). Contemporary research further delineates p53's governance of non-canonical processes, encompassing metabolic reprogramming, ferroptosis regulation, stem cell fate determination, autophagy, senescence, and tumor microenvironment modulation(X.-Y. Lin et al., 2023).

The co-occurrence of PIK3CA and TP53 mutations was predominantly identified in hormone receptor (HR)-negative and high-grade tumors, a finding consistent with prior investigations into residual disease following neoadjuvant chemotherapy(Rabab et al., 2025). Notably, the present analysis revealed a higher prevalence of HER2-positive tumors within this co-mutated subgroup than previously reported. The resultant molecular landscape, as defined by IHC-based subtyping, closely mirrored that of TP53-mutant breast cancer, with the Luminal B (HER2-positive) subtype being most frequent, followed by Luminal B (HER2-negative) and HER2-enriched disease. Genomically, tumors harboring both mutations exhibited a more complex mutational profile, with enriched alterations in genes such as ERBB2, CDK12, and NF1, suggesting an underlying genomic instability (Kim et al., 2016).

Critically, the concomitant presence of PIK3CA and TP53 mutations was associated with a significantly diminished response to neoadjuvant systemic therapy (NST) compared to tumors with TP53 mutations alone. This resistance was most pronounced in patients receiving taxane-based regimens, an observation further corroborated by computational genomic profiling (CGP) indicating reduced sensitivity to docetaxel, doxorubicin, and cisplatin. This suggests that the introduction of a PIK3CA mutation fundamentally alters therapeutic efficacy, effectively overriding any potential sensitivity linked to TP53 mutation status(Giorgi et al., 2015). While isolated PIK3CA mutations are established mediators of resistance to various therapies(Eustace et al., 2022), and certain TP53 mutations may paradoxically enhance sensitivity to DNA-damaging agents(Chen et al., 2019; Singh, 2023). Their co-mutation creates a particularly recalcitrant phenotype. Consequently, the PIK3CA mutation appears to be the dominant driver of chemoresistance in this genetic context. This finding underscores a critical therapeutic vulnerability, the retained susceptibility of PIK3CA-mutant tumors to α-selective and β-sparing PI3K inhibitors, presenting a promising avenue to overcome this acquired resistance.

The aggressive nature and poor prognosis associated with PIK3CA/TP53 co-mutation, further validated by large-scale cohorts like the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC), highlight a pressing clinical challenge. While the prognostic implications of individual TP53 or PIK3CA mutations are well-documented (AlFakeeh & Brezden-Masley, 2018; Glück et al., 2012). Evidence-based strategies specifically tailored for the co-mutated population remain scarce. This highlights the primary challenge in personalized oncology: identifying actionable therapeutic targets within complex molecular subsets. While tissue biopsy remains the diagnostic gold standard, its limitations in capturing tumor heterogeneity and its invasive nature complicate repeated assessments. In this context, advanced liquid biopsy methodologies, particularly the functional analysis of viable circulating tumor cells (CTCs) obtained via diagnostic leukapheresis, offer a transformative potential(Brandão et al., 2019; Faugeroux et al., 2020; Franken et al., 2021; Miricescu et al., 2020). These approaches could provide a dynamic, comprehensive understanding of tumor biology and mechanisms of resistance, ultimately guiding more effective and personalized treatment strategies for these high-risk patients.

However, we found no association between treatment in the DNA-binding domain and the prognosis of TNBC patients. Although TP53 status cannot predict the prognosis of individual patients, TNBC patients with discrepancies between TP53 expression and mutation status, particularly missense mutations with low expression levels, were found to have a poor prognosis. We can speculate that low expression in missense TP53 mutations is not caused by mutations, but by epigenetic changes in TP53, and these epigenetic changes may affect patient prognosis. However, we were unable to examine the post-transcriptional status of TP53, which is a limitation of our study (Kim et al. 2016).

Furthermore, patients treated with TP53 tended to have richer immunocyte infiltration and more active subsets in the TME compared to TP53-wt BC patients. Through further analysis, a possible mechanism linking TP53 mutations to immune checkpoint inhibitor (ICI) effectiveness was determined to be its vital role in the tumor immune microenvironment (Blagih et al. 2020; Zhang et al. 2021). Enrichment analysis results showed that the IL-17 signaling pathway was significantly altered in the TP53 mutant group, suggesting that TP53 mutations may be involved in TME reorganization. Previous studies have shown that in BC, IL-1β induces IL-17 expression from γδ T cells, resulting in neutrophil polarization. Nevertheless, IL-17 neutralization suppresses the T cell suppressor phenotype of neutrophils (Coffelt et al. 2015; Wu et al. 2020; Zhang et al. 2021).

## 4. CONCLUSION

Based on the synthesized evidence, it is conclusively demonstrated that TP53 mutations serve as a robust and consistent prognostic biomarker, strongly associated with aggressive tumor behavior, diminished survival outcomes, and altered therapeutic responses across various breast cancer subtypes. The co-occurrence of TP53 and PIK3CA mutations delineates a particularly adverse molecular subset, characterized by significantly worse progression-free survival and pronounced resistance to conventional neoadjuvant chemotherapy, especially taxanes, underscoring a deleterious synergistic effect. Furthermore, the functional consequence of TP53 mutations, rather than their mere presence, proves critically informative, as stratification by evolutionary action scoring and specific mutation characteristics reveals distinct phenotypic outcomes and can accurately predict genomic instability, such as homologous recombination deficiency. These findings collectively advocate for the integration of comprehensive molecular profiling, including nuanced TP53 and PIK3CA assessment, into clinical decision-making to enable refined risk stratification and guide the development of more effective, personalized treatment strategies for these high-risk patient populations.

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