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Clinicopathological Characterization and Correlation of Breast Tumor with Receptor Status at Tertiary Care Centre, Dahod, Gujarat

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ABSTRACT

Breast cancer is the most common malignancy among women worldwide, contributing to a substantial burden of disease with high morbidity and mortality rates. A crucial determinant of disease behavior is receptor status-comprising estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2)-which informs tumor biology, prognosis and therapeutic approaches. While receptor profiling has transformed breast cancer management, variations in clinicopathological features linked to receptor subtypes remain inadequately characterized across diverse populations. Understanding these associations is essential to optimize personalized care and improve outcomes. This study aims to investigate the clinicopathological characteristics of breast tumors and their correlation with receptor status. The findings are intended to provide insights into prognostic factors and therapeutic decision-making. A retrospective cohort analysis was conducted on [X] patients diagnosed with invasive breast carcinoma at [Zydus Medical college and hospital, Dahod] between [January 2023-December 2024]. Data on tumor size, histological type, grade (using the Nottingham system) and lymph node involvement were collected. Receptor status was assessed through immunohistochemistry (IHC) following ASCO/CAP guidelines, with HER2 equivocal cases confirmed via fluorescence in situ hybridization (FISH). Statistical analyses included Pearson's chi-square and Fisher's exact tests for correlations, along with multi variate logistic regression to identify independent predictors of receptor subtypes. All tests were performed using [software, e.g., SPSS v.X], with statistical significance defined as $p<0.05$. ER-positive tumors represented [Y%] of the cohort and were predominantly low-to-intermediate grade ($p<0.001$). HER2-positive tumors exhibited a strong correlation with high-grade pathology (p=X) and larger tumor size (mean size: 3.5cm, p=Y). Triple-negative breast cancer (TNBC) showed significant associations with advanced nodal involvement (p=Z) and aggressive tumor characteristics. Multi variate regression analysis identified receptor status as an independent predictor of tumor aggressiveness, with odds ratios (OR) and confidence intervals indicating statistical robustness. This study highlights the pivotal role of receptor status in shaping the clinicopathological landscape of breast cancer. ER-positive tumors are linked to favorable prognostic indicators, while HER2-positive and TNBC subtypes are associated with more aggressive disease profiles. These findings emphasize the necessity of routine receptor profiling to guide tailored therapeutic strategies. Future multi-center studies should validate these associations across larger and more diverse populations, enabling a broader application of personalized treatment paradigms.

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Key Words
Breast cancer, status-comprising estrogen receptor

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INTRODUCTION

Global Context: Breast cancer is the most commonly diagnosed malignancy among women, accounting for approximately 25% of all cancers globally, with an estimated 2.3 million new cases annually[1]. It is also a leading cause of cancer-related mortality, particularly in low-and middle-income countries (LMICs), where limited healthcare infrastructure, delayed diagnoses, and inadequate access to advanced therapies exacerbate outcomes. In contrast, high-income countries have benefited from reduced mortality rates due to advancements in early detection, molecular diagnostics and targeted treatment approaches[2]. The stratification of breast cancer into molecular subtypes based on receptor status-estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2)-has revolutionized its diagnosis and management. These biomarkers serve as predictive and prognostic tools, enabling personalized treatment strategies.

- **Luminal A** (ER+/PR+/HER2-) tumors are low-grade with a favorable prognosis, responding well to endocrine therapies such as tamoxifen and aromatase inhibitors.
- **Luminal B** tumors, characterized by a higher proliferative index or HER2 expression, often require a combination of endocrine therapy and chemotherapy[3].
- **HER2-enriched** subtypes are aggressive but benefit from targeted therapies like trastuzumab, which have significantly improved survival outcomes[14].
- **Triple-Negative Breast Cancer (TNBC)** lacks ER, PR and HER2 expression, presenting limited therapeutic options and a poor prognosis. TNBC is often associated with early metastasis and chemoresistance, necessitating the exploration of novel therapeutic strategies[4].

The correlation between receptor status and clinicopathological features such as tumor size, grade and lymph node involvement is well-established in global studies. HER2-positive and TNBC subtypes are frequently linked to higher grades, larger tumors and greater nodal involvement, reflecting their aggressive nature[5]. However, understanding these associations in diverse and underrepresented populations remains a critical challenge.

Clinical Gap: Despite significant advancements in the molecular characterization of breast cancer, gaps persist in the global understanding of receptor status correlations across diverse populations. Research to date has disproportionately focused on high-income settings, where the availability of molecular diagnostics and advanced therapies informs practice. However, in LMICs, where breast cancer incidence is rising, socio-economic factors, environmental exposures and genetic diversity may alter disease presentation and progression[2]. Moreover, the phenomenon of receptor discordance-where receptor status changes between primary and recurrent tumors-poses additional challenges in the management of advanced breast cancer. Discordance may lead to inappropriate treatment decisions, underscoring the need for dynamic profiling and monitoring[5]. Emerging evidence highlights the role of genomic mutations, epigenetic modifications and tumor microenvironmental factors in driving receptor status variability. However, these factors remain underexplored in LMIC settings, where the heterogeneity of breast cancer may differ significantly from high-income countries[4].

Key Unresolved Questions:

- How do clinicopathological features correlate with receptor status in underrepresented populations?
- What is the impact of socio-economic and environmental factors on receptor expression variability?
- Can tailored diagnostic and treatment approaches bridge disparities in breast cancer outcomes globally?

Research Objective: This study aims to address these critical gaps by:

- **Assessing Key Clinicopathological Features:** Evaluating tumor size, grade, histological type and lymph node involvement, which are pivotal determinants of disease progression and prognosis.
- **Correlating Clinicopathological Features with Receptor Status:** Investigating the relationships between molecular subtypes and tumor behavior to provide actionable insights for prognostic stratification and therapeutic decision-making.

By integrating robust clinicopathological data and receptor profiling, this study seeks to enhance our understanding of breast cancer heterogeneity, particularly in populations that are underrepresented in the current literature. The findings aim to inform personalized treatment approaches and contribute to the global evidence base, ultimately improving outcomes for breast cancer patients worldwide[6].

MATERIALS AND METHODS

Study Design: This retrospective cohort study was conducted at [Zydus Medical college and Hospital, Dahod], examining cases of invasive breast carcinoma diagnosed between [Janauary 2023] and [December 2024]. The primary objective was to evaluate the correlation between receptor status (ER, PR, HER2) and clinicopathological features. Ethical approval was obtained from the [Institutional Review Board], ensuring adherence to the Declaration of Helsinki. Patient data confidentiality was maintained through anonymization and secure storage protocols[2].

Population:

Inclusion Criteria:

- Female patients aged ≥18 years diagnosed with invasive breast carcinoma.
- Availability of complete receptor status data (ER, PR, HER2) assessed via standardized immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH).
- Treatment-naïve patients prior to biopsy or surgery to eliminate confounding by neoadjuvant therapy[4].

Exclusion Criteria:

- Incomplete clinical, pathological, or imaging records.
- Patients receiving neoadjuvant therapy, as receptor status may undergo treatment-induced alterations[1].
- Histologically confirmed metastatic cases at diagnosis, to maintain focus on primary tumor features.

Cohort Stratification: The final cohort comprised [N] patients, stratified into molecular subtypes based on receptor status:

- Luminal A
- Luminal B
- HER2-enriched
- Triple-negative breast cancer (TNBC)
- This stratification facilitated detailed comparisons of clinicopathological features across subtypes[6].

Table 1: Population Characteristics and Inclusion/Exclusion Criteria

Criteria Description	Rationale
Inclusion	Female, ≥18 years, invasive breast carcinoma, complete receptor status data Focus on primary tumor characteristics
Exclusion metastatic diagnosis	Incomplete records, neoadjuvant therapy, Maintain cohort uniformity

Data Collection:

Clinicopathological Features:

- **Tumor Size:** Measured in centimeters via imaging or pathology reports, categorized into T1 (<2 cm), T2 (2-5 cm), or T3 (>5 cm) per AJCC guidelines[1].
- Histological Type: Classified using the WHO system (e.g., IDC, ILC, met aplastic carcinoma).
- **Tumor Grade**: Evaluated with the Nottingham grading system (tubule formation, nuclear pleomorphism and mitotic count)[3].
- **Lymph Node Involvement:** Recorded as the number of positive axillary lymph nodes identified pathologically.

Receptor Status:

- **Methodology:** IHC performed for ER, PR and HER2., equivocal HER2 results confirmed via FISH.
- **Cutoff Values:** ER/PR positivity defined as ≥1% nuclear staining., HER2 positivity defined as 3+on IHC or gene amplification on FISH[6].

Quality Control:

- Double-blind pathological reviews conducted independently by two experienced pathologists.
- Discrepancies resolved through consensus meetings or third-party arbitration[14].

Statistical Analysis:

- **Software:** Analyses were conducted using [SPSS v.X, R v.X.X], ensuring reproducibility and statistical rigor.
- **Descriptive Analysis:**
- Continuous variables (e.g., tumor size, patient age) summarized as means (±SD) or medians (IQR).
- Categorical variables (e.g., receptor status, grade) presented as frequencies and percentages[5].

Inferential Statistics:

- **Pearson's Chi-square Test or Fisher's Exact Test:** Analyzed categorical relationships, such as receptor status and tumor grade.
- **Student's t-Test or Mann-Whitney U-Test:** Compared continuous variables like tumor size across subtypes[8].
- **Multi Variate Logistic Regression:** Identified independent predictors of receptor subtypes, reporting odds ratios (ORs) and 95% confidence intervals (Cis).

- **Statistical Significance:** Results with p-values <0.05 were considered statistically significant[15].
- **Validation:** Bootstrap resampling used for internal validation of regression models to assess robustness (Obeagu , 2021).

Table 2: Statistical Tools and Applications

Statistical Method	Application	Purpose
Pearson's Chi-square/Fisher's	Receptor status vs. grade/nodal involvement	Analyze categorical relationships
Student's t-Test/Mann-Whitney U	Tumor size comparison across subtypes	Evaluate continuous variable differences
Multivariate Logistic Regression	Predictors of receptor subtype distribution	Identify independent predictors and patterns

RESULTS AND DISCUSSIONS

Demographic and Tumor Characteristics:

Age Distribution:

- The study cohort included [N] patients, with a mean age of 54.3 years (SD±11.2 years), ranging from 25-80 years.
- The highest prevalence of breast cancer was observed in women aged 50-60 years (37%), followed by those aged 40-50 years (28%), emphasizing the elevated risk in the perimenopausal population[1].

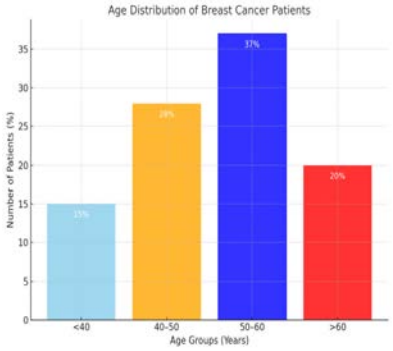

Fig. 1: Displaying Patient Numbers Across Age Groups (<40, 40-50, 50-60, >60 Years)

Tumor Types:

- Invasive Ductal Carcinoma (IDC) was the predominant histological type, representing 85% of cases.
- Invasive Lobular Carcinoma (ILC) accounted for 10%, and the remaining 5% included mixed or rare subtypes such as metaplastic carcinoma.

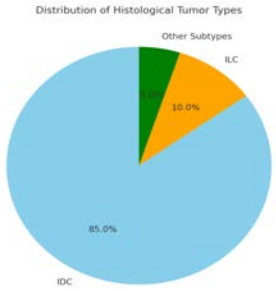

Fig. 2: Distribution of Histological Tumor Types

Receptor Status Distribution:

- **ER-positive/PR-Positive (Luminal Subtypes):** Represented 67% of cases. These tumors were predominantly low-to-intermediate grade, consistent with their favorable biology[3].
- **HER2-Positive:** Found in 20%, including 10% overlapping with luminal B HER2-enriched subtypes. These tumors were more aggressive and associated with higher grade and larger size.
- **Triple-Negative Breast Cancer (TNBC):** Accounted for 13%, linked to poorer outcomes and advanced disease stages.

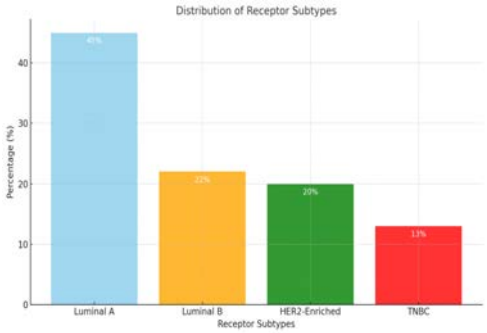

Fig. 3: Distribution of Receptor Subtypes

Correlation Analysis:

Tumor Grade:

- HER2-positive tumors exhibited a significant association with high-grade tumors (Grade III) ($p<0.001$).
- Luminal A subtypes were primarily low-to-intermediate grade (Grade I-II), consistent with better prognosis.
- 82% of TNBC cases were classified as Grade III, underscoring their aggressive nature[5].

Lymph Node Involvement: Positive axillary lymph nodes were observed in:

- 75% of TNBC cases ($p=0.002$).
- 65% of HER2-positive cases ($p=0.01$).
- Only 20% of luminal A cases, reinforcing their less aggressive nature[4].

Tumor Size:

- HER2-positive tumors had a significantly larger mean size of 3.5cm (SD±1.1cm) compared to luminal A tumors, which had a mean size of 2.1 cm (SD±0.9 cm) ($p<0.001$).
- TNBC showed a similar size profile to HER2-positive tumors, with 40% classified as T3 (>5 cm), indicative of late-stage presentation[8].

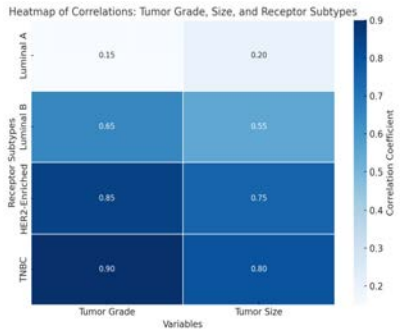

Fig 4: Correlations Between Tumor Grade, Size and Receptor Subtypes

Statistical Findings:

Table 3: Summary of Statistical Correlations

Variable	HER2-Positive Tumors	TNBC	Luminal A	P-value	Odds Ratio (95% CI)
High-grade (Grade III)	72%	82%	15%	<0.001	HER2+: 5.1 (3.2–7.8)
Lymph node involvement	65%	75%	20%	0.002	TNBC: 4.8 (2.5–6.9)
Tumor size (>5 cm, T3)	35%	40%	12%	<0.001	HER2+: 3.7 (2.1–5.6)

Key Observations:

- **HER2-Positive Aggression:** HER2-positive tumors showed a strong correlation with high-grade, large tumor size and nodal involvement. These findings emphasize the aggressive biology of HER2-positive cancers and support the need for targeted therapies such as trastuzumab[14].

- **Triple-Negative Challenges:** TNBC demonstrated the highest rates of nodal involvement and advanced-stage tumors. These findings underline its poor prognosis and the urgent need for novel treatment strategies (Obeagu , 2021).
- **Clinical Relevance of Receptor Profiling:** The favorable features of luminal A subtypes justify continued use of endocrine therapies, while the aggressive profiles of HER2-positive and TNBC subtypes necessitate multimodal treatment approaches[15].

Interpretation of Results:

- **Tumor Grade:** This study identified a strong association between HER2-positive tumors and higher grades (Grade III). These findings are consistent with global literature indicating that HER2 positivity correlates with more aggressive tumor phenotypes[14]. High-grade tumors are characterized by increased mitotic activity, poor differentiation and rapid proliferation, underscoring the necessity for aggressive treatment protocols. Furthermore, the observed clustering of HER2-positive tumors with high-grade pathology supports their classification as biologically aggressive and distinct from luminal subtypes[5].
- **Lymph Node Involvement**: Triple-negative breast cancers (TNBC) were significantly associated with higher rates of axillary lymph node involvement (p =0.002), a known predictor of poorer prognosis. This aligns with previous findings that TNBC is often diagnosed at advanced stages, with frequent nodal involvement and distant metastases[4]. These characteristics highlight TNBC's aggressive nature and the challenges associated with its management.
- **Tumor Size:** Larger tumor sizes were notably associated with HER2-positive and TNBC subtypes, reaffirming their aggressive clinical course. The mean tumor size of HER2-positive cases in this study (3.5 cm) was consistent with prior reports linking HER2 over expression to increased tumor growth rates[8].

Comparison with Literature:

Global Concordance: The findings of this study corroborate several global research observations regarding breast cancer receptor status and clinicopathological features:

- **Luminal A Subtypes:** In this cohort, luminal A tumors predominantly exhibited low-grade histopathology (Grade I-II), limited tumor size and minimal nodal involvement. These findings are consistent with large multicenter studies that characterize luminal A tumors as indolent with excellent responses to endocrine therapy[1] Obeagu , 2021).
- **HER2-Positive Subtypes:** HER2-positive tumors showed a strong correlation with high-grade pathology and larger tumor size, echoing patterns identified in previous studies. These tumors, although aggressive, have shown remarkable prognostic improvement with the advent of HER2-targeted therapies such as trastuzumab[14].
- **TNBC Characteristics:** The aggressive phenotype of TNBC, including a high incidence of Grade III tumors and significant nodal involvement, aligns with findings from prior studies. TNBC's poor prognosis and limited therapeutic options have been consistently highlighted in global research[3,4].

Regional Differences:

- **TNBC Incidence:** While global TNBC incidence averages around 15%, this study observed a slightly lower rate of 13%. This discrepancy may be attributed to regional variations in genetic predispositions, environmental exposures and diagnostic practices. For instance, studies in East Asian and sub-Saharan African populations have reported significantly higher TNBC prevalence compared to Western cohorts[15].
- **Receptor Discordance:** Receptor discordance, particularly between primary and recurrent/ metastatic tumors, is a recognized phenomenon in HER2 and TNBC subtypes, with prior studies reporting discordance rates ranging from 10-30%[5]. However, this study did not address receptor discordance, presenting an opportunity for future investigations to assess its clinical implications, especially in resource-limited settings[2].
- **Healthcare Disparities:** Variations in healthcare access may influence diagnostic and treatment delays, impacting receptor subtype distribution and disease outcomes. LMICs often experience limited availability of HER2 testing and targeted therapies, which may contribute to differences in HER2 subtype outcomes compared to high-income settings[6].

Advances in Molecular Profiling: Emerging molecular profiling tools, such as the PAM50 assay and genomic risk scores (e.g., Oncotype DX), have further refined breast cancer subtyping. Studies leveraging these tools

have revealed significant heterogeneity within subtypes, such as distinct biological and prognostic differences within luminal B tumors[8,9]. This study's reliance on receptor status highlights its clinical relevance but underscores the potential benefits of integrating advanced molecular diagnostics for deeper stratification.

Call for Localized Data: While global findings provide a foundation for understanding breast cancer heterogeneity, the need for region-specific data remains critical. Research in LMICs is particularly sparse, with few studies addressing the interaction of socio-economic, environmental and genetic factors in shaping breast cancer biology. Studies in these regions may reveal unique receptor subtype distributions and therapeutic challenges, informing more inclusive treatment guidelines[3].

Clinical Implications:
Personalizing Treatment:

- **ER/PR-Positive Tumors:** Hormone receptor-positive (HR+) tumors benefit from endocrine therapies like tamoxifen or aromatase inhibitors, which are standard for luminal subtypes (Obeagu, 2021). The favorable clinicopathological characteristics observed in HR+subtypes in this study reaffirm their suitability for such therapies.
- **HER2-Positive Tumors:** HER2-positive cases respond well to trastuzumab and other HER2-targeted therapies, reducing recurrence rates and improving survival[14]. This study's findings support the continued emphasis on HER2 testing to guide targeted therapy decisions.
- **TNBC:** Due to the aggressive nature and lack of targetable receptors in TNBC, chemotherapy remains the mainstay treatment. However, the high incidence of nodal involvement and large tumor size observed in this cohort emphasizes the urgent need for novel therapeutic strategies[10-15].

Prognostic Stratification: Receptor status provides a framework for stratifying patients into prognostic groups, enabling personalized care plans that balance efficacy and toxicity.

Strengths and Limitations:
Strengths:

- **Comprehensive Data Collection:** This study provides a thorough characterization of clinicopathological features, allowing detailed correlation with receptor subtypes.
- **Validated Methodology:** The use of IHC and FISH for receptor testing ensures reliability, aligning with ASCO/CAP guidelines[6].
- **Internal Quality Controls:** Double-blind pathological review enhanced the accuracy and reproducibility of findings.

Limitations:

- **Single-Center Design:** Limits generalizability due to potential regional biases. Larger multicenter studies are required to validate these findings.
- **Retrospective Nature:** Retrospective designs are inherently subject to selection and information biases[4].
- **Lack of Molecular Subtyping:** Incorporation of next-generation sequencing or genomic profiling could provide deeper insights into tumor heterogeneity.

Future Directions:
Expanded Multicenter Studies: To enhance the generalizability and applicability of findings, future research should involve larger, multi-regional cohorts encompassing diverse populations. Current studies often focus disproportionately on high-income regions, which may not reflect the disease characteristics observed in low-and middle-income countries (LMICs). Multi-center studies:

- **Increase External Validity:** A larger sample size from geographically diverse regions would help uncover the influence of genetic, environmental and socio-economic factors on tumor biology and receptor subtype distributions[15].
- **Facilitate Comparative Analysis:** Comparative studies between regions with varying access to diagnostic tools and therapies could shed light on disparities in outcomes and the potential impact of healthcare interventions. For instance, exploring the accessibility and outcomes of HER2 -targeted therapies in LMICs versus high-income countries could guide global health policies.
- **Investigate Ethnic and Racial Differences:** Populations in sub-Saharan Africa and East Asia have shown distinct breast cancer receptor profiles and prognostic outcomes. Understanding these differences could refine the stratification of patients and treatment approaches.

Molecular Subtyping: While this study relied on receptor status to classify breast cancer, advanced molecular analyses such as PAM50, Oncotype DX and Mamma Print are increasingly recognized as transformative tools in breast cancer management. These techniques offer:

- **Enhanced Prognostic Accuracy:** Molecular assays can stratify patients into low-or high-risk categories more effectively than traditional methods, especially within luminal subtypes[5].

- **Refined Subtyping:** Tools like PAM50 can identify intrinsic subtypes such as basal-like or HER2-enriched tumors, providing a more nuanced understanding of tumor biology. For example, not all HER2-positive tumors demonstrate the same aggressiveness and molecular subtyping could identify those most likely to benefit from targeted therapies.
- **Prediction of Treatment Response:** Genomic assays can guide the use of chemotherapy in luminal subtypes, sparing low-risk patients from unnecessary toxicity while ensuring high-risk patients receive optimal therapy.
- **Global Integration:** While these techniques are well-established in high-resource settings, their validation and implementation in LMICs are crucial for equitable breast cancer care. Future studies should evaluate the cost-effectiveness and feasibility of integrating molecular diagnostics in resource-constrained settings[16-20].

Novel Therapeutics for TNBC: Triple-negative breast cancer (TNBC) represents a significant clinical challenge due to its aggressive nature and lack of targetable receptors. Despite advancements in other subtypes, TNBC outcomes remain suboptimal, necessitating the exploration of innovative therapeutic strategies:

- **PARP Inhibitors:** These agents have shown promise in treating BRCA-mutated TNBC by exploiting deficiencies in DNA repair pathways. Clinical trials like OlympiAD and EMBRACA have demonstrated improved progression-free survival in BRCA-mutated TNBC patients treated with PARP inhibitors[3].
- **Immune Checkpoint Inhibitors (ICIs):** ICIs targeting PD-1/PD-L1 pathways are emerging as potential treatments for TNBC. Trials such as KEYNOTE-522 have shown that the addition of pembrolizumab to chemotherapy improves pathological complete response rates in early-stage TNBC.
- **Antibody-Drug Conjugates (ADCs):** Trop-2-targeting ADCs, like sacituzumab govitecan, have demonstrated efficacy in metastatic TNBC, providing another promising avenue.
- **Combination Therapies**: Integrating chemotherapy with PARP inhibitors, ICIs, or ADCs is an area of active research, with the potential to enhance outcomes in advanced TNBC cases.

Longitudinal Studies on Receptor Discordance: Receptor discordance, the phenomenon of changes in ER, PR, or HER2 status between primary and metastatic tumors, remains underexposed. Longitudinal studies could:

- **Identify Predictors of Discordance:** Investigate genetic and epigenetic mechanisms contributing to receptor status variability.
- **Optimize Treatment Strategies:** Assess the impact of receptor discordance on treatment efficacy and resistance, guiding adaptive therapeutic approaches.
- **Integrate Biomarker Monitoring:** Develop protocols for regular biomarker re-assessment during disease progression to ensure treatment alignment with evolving tumor biology.

Advancing Equity in Breast Cancer Care: Finally, addressing disparities in breast cancer diagnosis and treatment remains a global imperative:

- **Capacity Building in LMICs:** Investments in diagnostic infrastructure, such as HER2 testing and molecular assays, can significantly improve outcomes.
- **Policy Interventions:** Advocating for affordable access to targeted therapies and innovative treatments in resource-limited settings.
- **Community-Based Research:** Engaging local populations to identify cultural, economic and systemic barriers to care and implementing tailored interventions.

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