REVIEW

IHC/FISH concordance and prognostic value of microarray-based genomic profiling tests in breast cancer molecular subtyping: A systematic review

Nash Daniel Silava[Δ1], Elgin Paul Quebral[Δ2], Eric David Ornos[3], Vivien Josol[4], Dominic Karl Bolinas[5], Karol Ann Baldo[5], Abialbon Francisco[6], Apple Valparaiso[1], and Sheriah Laine de Paz-Silava*[2]

[1]Department of Surgery, Philippine General Hospital, University of the Philippines Manila, Ermita, Manila, 1000 Philippines
[2]Virology Laboratory, Department of Medical Microbiology, College of Public Health, University of the Philippines Manila, Ermita, Manila, 1000 Philippines
[3]Department of Medicine, Philippine General Hospital, University of the Philippines Manila, Ermita, Manila, 1000 Philippines
[4]Lung Center of the Philippines, Diliman, Quezon City, 1100 Philippines
[5]College of Medicine, University of the Philippines Manila, Ermita, Manila, 1000 Philippines
[6]Department of Veterinary Paraclinical Sciences, College of Veterinary Medicine, University of the Philippines Los Baños, College, Los Baños, Laguna, 4031 Philippines

[Δ]Co-First Authors

ABSTRACT

Breast cancer is a major public health concern worldwide. Accurate molecular subtyping is essential for appropriate patient management. Conventional pathology-based (immunohistochemistry/fluorescence in situ hybridization, IHC/FISH) tests have been the cornerstone of molecular subtyping, but newer genomic-based microarray techniques have shown promise to better classify tumors. Therefore, we aimed to systematically review the concordance and prognostic value of microarray-based breast cancer subtyping techniques. Scopus, Google Scholar, PubMed and Cochrane databases were systematically searched according to PRISMA guidelines. Articles comparing IHC/FISH- and microarray-based subtyping were included. Data on concordance, treatment response, and survival outcomes were extracted and analyzed. Independent reviewers assessed all articles against the inclusion and exclusion criteria. The concordance of microarray with IHC/FISH varied in the selected 45 articles. Studies using TargetPrint reported up to 100% concordance while one PAM50 study reported concordance rates as low as 54–60%. Some BluePrint-based microarray assays reclassified approximately 18% of luminal tumor to basal type, and 5% of ER+HER2- tumors to basal type. Microarray-based technologies have shown potential in prognosticating treatment outcomes and survival, and they may enhance breast cancer subtyping and improve the prediction of clinical outcomes. Future directions should focus on the standardization of microarray-based subtyping techniques and validating their clinical utility in various populations.

*Corresponding author
Email Address: **smdepaz@up.edu.ph**
Date received: 13 June 2025
Dates revised: 14 November 2025, 23 December 2025
Date accepted: 30 December 2025
DOI: https://doi.org/10.54645/2026191JVJ-47

INTRODUCTION

Breast cancer remains a leading cause of disease burden worldwide. Globally, it is second to lung cancer in incidence, with 2.3 million new cases. It was also the fourth leading cause of cancer-related deaths with 665,000 deaths in 2022 (Bray *et al*., 2024). In women, it remains the most diagnosed cancer and the leading cause of cancer death, accounting for approximately one in four cancer cases and one in six cancer deaths in women worldwide. In 2020, the global prevalence was 7.8 million in women with 685,000 deaths (Lei *et al*., 2021). Since the 1980s,

KEYWORDS

breast neoplasms, microarray, immunohistochemistry, fluorescence *in situ* hybridization

there has been a decline in breast cancer death rates and an increase in the incidence rates worldwide. Age-standardized breast cancer mortality in developed countries has dropped by 40% in the past 40 years, and this has been attributed to advances in breast cancer early detection, timely diagnosis, and comprehensive treatment. The strategies to improve these outcomes rely on the fundamental health systems to deliver the appropriate treatment. Dramatic technological advancements in the field of molecular medicine in the last decade have been a game-changer in providing up-to-date clinical practice guidelines on breast cancer and other diseases (Ortega *et al*. 2024, Sifakis *et al*. 2024).

The knowledge on breast cancer and its treatment has progressed rapidly with novel innovations such as immunohistochemistry/fluorescence in situ hybridization (IHC/FISH) studies. These advancements in molecular characterization gave rise to breast cancer neoadjuvant therapies and hormonal treatments through the detection of estrogen receptor (ER), progesterone receptor (PR), and human epithelial growth factor receptor 2 (HER2). Depending on the presence or absence of these receptors, patients are classified into their corresponding molecular subtypes. These subtypes, as defined by the St. Gallen consensus on primary therapy of early breast cancer, helps guide the clinician towards personalized treatment (Harbeck *et al*., 2013). For example, triple-negative breast cancer (TNBC), a biological and heterogeneous subtype, is more common among younger women and those carrying a BRCA1 gene mutation. These patients are not eligible for endocrine or HER2-targeted therapy; thus, chemotherapy remains as the remaining treatment option along with surgery (Bernemann *et al*. 2014). While many patients may have the option to proceed with surgery or neoadjuvant chemotherapy, patients with TNBC benefit from neoadjuvant chemotherapy with 40-50% achieving a pathologic complete response (pCR) after treatment (Van Den Ende *et al*. 2023). Hence, it is important to ensure accurate classification of patients to ensure proper treatment leading to more favorable outcomes.

To address this issue, molecular medicine approaches have been increasingly utilized to provide more appropriate management for breast cancer patients. In fact, newer breast cancer molecular subtyping technologies were key players in revamping the St. Gallen consensus, a major clinical practice guideline for breast cancer management. The recent 2023 St. Gallen International Breast Consensus Conference pushed for more personalized management based on the recent findings on more advanced breast cancer molecular subtyping. Using these newer technologies for molecular subtyping, several studies highlighted differences from the usual conventional IHC/FISH-based classifications (Curigliano *et al*. 2023).

In recent years, newer genomic profiling tests based on microarray technology have emerged as new tools in molecular subtyping. Microarray technology can assess and determine simultaneously the genetic expression profiles across different genes in cancer cells (Sarhadi *et al*. 2024). Conventional IHC/FISH, in contrast, is limited to assessing only one to a few biomarkers. It is also important to consider that such histopathology-based methods, which rely mainly on the presence or absence of protein biomarkers, do not reflect the multigene signatures that can be seen in breast cancer tissue (Zubair, Wang & Ali 2021). Thus, this limitation of IHC/FISH can be assessed using gene-expression studies (e.g. microarray), which can characterize multiple pathways by analyzing heatmaps of upregulated and downregulated genes associated with breast cancer (Zubair, Wang & Ali 2021). Moreover, the genetic expression profiles in cancer cells may not always be concordant with what can be observed through IHC/FISH results. Several clinical studies have explored the utility of microarray technology as well in the management of breast cancer. In this review, we aimed to determine the role of microarray-based genomic profiling tests in breast cancer subtyping by reviewing its concordance with conventional IHC/FISH methods and its prognosticating value on clinical outcomes such as therapy response rates and survival.

MATERIALS AND METHODS

Search Strategy

The systematic review was accomplished in October to December 2023 in accordance with the updated Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. There was no restriction on publication date included in the search. A comprehensive systematic search of Scopus, PubMed, Cochrane, and Google Scholar was performed. The search strategies incorporated the population, intervention, comparator, and outcome (PICO) in this study. The search was restricted to research published in the English language. The search strategy used is shown in Table 1.

Table 1: Search strategy for the systematic review.

((breast cancer*) OR (breast carcinoma) OR (breast neoplasm*) OR (mammary neoplasm*) OR (mammary cancer*) OR (mammary carcinoma*) OR (breast tumor*) OR (breast malignant tumor) OR (breast malignanc*) OR (mammary tumor) OR (mammary malignanc*) OR (breast malignant tumor) OR (mammary malignant tumor)) AND
(((microarray*) or (microarray analysis)) AND ((molecular* subtyp*) OR (molecular subtyping) OR (molecular subtypes))) AND
(FISH Techni*) OR (Fluorescent in Situ Hybridization*) OR (Fluorescence in Situ Hybridization*) OR (Immunocytochemistr*) OR (immunohistochemistr*) AND
diagnosis OR diagnoses OR diagnostic* OR concordan* OR discordan* OR prognosis OR prognoses OR prognostic* OR survival OR response* OR outcome*

Operational definition of terms

In this systematic review, the operational definitions of concordance, response to therapy and survival were defined. Concordance is defined as agreement or consistency between IHC/FISH and microarray technique, usually presented as a percentage of similarity in results or as percent disagreement or discordance. Response to therapy is defined as the outcome of a patient after undergoing chemotherapy, neoadjuvant chemotherapy, radiation therapy, and/or surgery, usually expressed as clinical complete response (cCR) or pCR rates, used to determine the prognostic value of microarray technology. Survival is defined as the state of being alive, usually measured after a defined number of years after diagnosis or treatment and sometimes expressed as survival rate or mortality rate.

Inclusion and Exclusion Criteria

The current study included quantitative studies, including observational study designs such as cross-sectional, case-control and cohort studies, and interventional study designs like randomized controlled trials and nonrandomized controlled trials. Narrative reviews, commentaries, editorials, letters, position papers and mini-reviews, case-series, case reports, and experimental studies such as laboratory and *in silico*-based researches were excluded from the study. The inclusion criteria are as follows: (1) enrollment of adult (age ≥ 18 years old) patients with breast cancer; (2) utilized a microarray-based genomic profiling technology for molecular subtyping of breast cancer tissue; (3) assessed subtyping for estrogen receptor (ER), progesterone receptor (PR), HER2, luminal A, luminal B, or basal type; (4) used conventional IHC/FISH for subtyping as comparator; and (5) assessed at least one outcome of the three

outcome measures (concordance of breast cancer subtype classification, response to therapy, survival or mortality). On the other hand, the exclusion criteria are as follows: (1) use of specimens other than breast tissue (e.g. cell free DNA in plasma); (2) use of a novel IHC/FISH technique that is not previously validated clinically as comparator; and (3) enrolled patients that have metastatic disease at baseline, patients with prior chemotherapy, radiotherapy, or endocrine therapy, or with concurrent uncontrolled infections or uncontrolled comorbid disease. For articles that did not mention the age of patients from which samples were taken, the studies were still included since most breast cancer cases are seen in the adult population.

Selection of Studies

The selection process involved two phases: (1) title and abstract screening; and (2) full-text review. Two authors independently reviewed the selected articles using the inclusion and exclusion criteria. The decision to include the article was reached through a consensus. In case a consensus could not be made, consultation with a third author was done.

Data Extraction

Data from the selected studies were extracted using standardized data collection spreadsheets. Extracted information included study title, authors, year, country, study design, description of study population, sample size, and outcomes**.** Main information that was extracted and reported included the type of microarray technology used, the concordance estimates between IHC/FISH and the microarray technology in classifying the patients to molecular subtypes (e.g., Luminal A, Luminal B, HER2-enriched, basal, estrogen/progesterone/hormone receptor positive). Data on the prognostic value of microarray technology to determine response to therapy (including but not limited to chemotherapy, radiation therapy, and/or surgery) and survival or mortality rates were also retrieved.

Synthesis and Analysis

The data were synthesized through a narrative review, accompanied by a summary table. Other data included the number of published research papers per country, the number of publications per year, and the frequency of various microarray technologies used.

RESULTS AND DISCUSSION

Breast cancer imposes a substantial global disease burden, with most of the cases being diagnosed at advanced stages. Clinicians screen patients and often recommend surgery or neoadjuvant treatment. This decision considers breast cancer subtype classification, which is conventionally done with IHC/FISH. For management to be effective, it is important to classify patients accurately to subtypes that reflect the tumor biology. This study investigated the concordance and prognostic value of microarray-based tests with conventional subtype classification.

Figure 1 shows the PRISMA flow diagram of this systematic review. A total of 1,006 articles were retrieved from the database search, with 840 remaining after deduplication (Figure 1). After screening the titles and abstracts, 164 articles were selected. Most papers that were excluded focused on gene expression studies and research unrelated to microarray technology. After full-text analysis, 45 articles were selected for inclusion in the review.

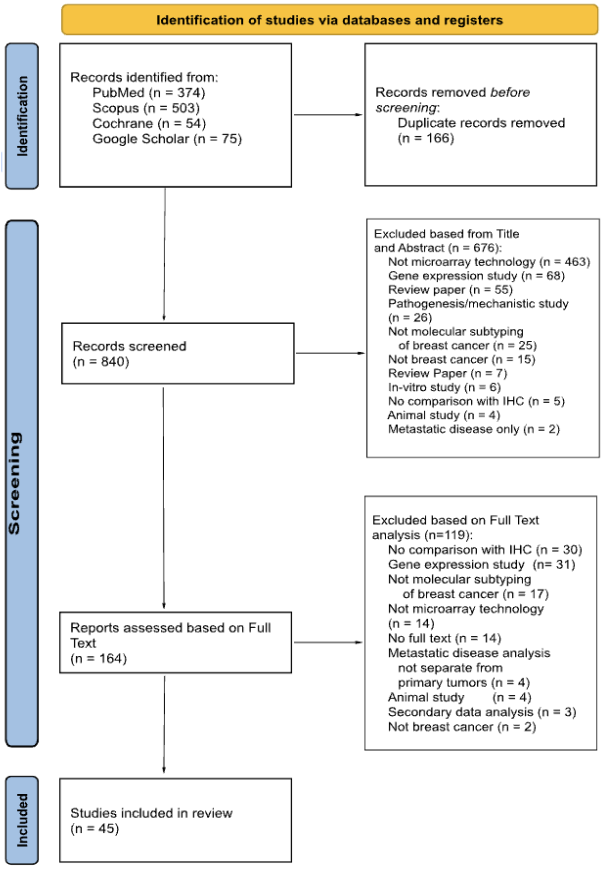

Figure 1: PRISMA flow diagram for the selection of included and excluded articles in the study. A total of 1006 publications were identified, where 166 duplications were removed. After rigorous screening, 795 studies were excluded. The total number of published articles included in the review is 45.

Figure 2 maps out the distribution of included studies examining microarray technology in the molecular subtyping of breast cancer. As shown in Figure 2, most of the studies included the European population (28/45, 62%), but the United States of America (USA) was the country that was most represented (11/45, 24%), followed by the Netherlands (10/45, 22%). A few more others were done in the South American and South African region. Asian countries were less represented except for a few ones done in Japan, South Korea, Singapore, China and some countries in the Middle East.

Figure 2: Distribution of studies that investigated microarray technology for breast cancer subtyping across different countries. The size of the circle reflects the number of studies that investigated the population of the country. The graph was created with Datawrapper.

Figure 3 depicts the number of publications on microarray technology for breast cancer subtyping over time. There was a trend towards an increasing number of studies since 2008, with most of the publications done in the past ten years (Figure 3). Meanwhile, Figure 4 shows the distribution of microarray-based platforms that were used for subtyping of the included studies. A total of ten different microarray technologies were investigated among the papers (Figure 4). One-third of which investigated the PAM50 technology (18/54, 33.3%) followed by BluePrint (10/54, 18.5%), MammaPrint (8/54, 14.8%) and TargetPrint (7/54, 13.0%). Key findings of the studies are found in Table 2 and discussed in the succeeding section.

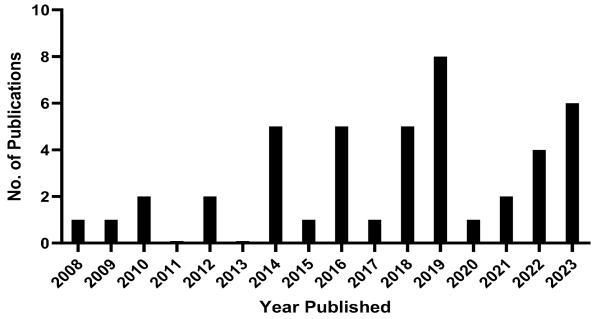

Figure 3: Number of publications on the use of microarray technology for breast cancer subtyping through the years. Most published articles included in the study were published in 2019 and 2023.

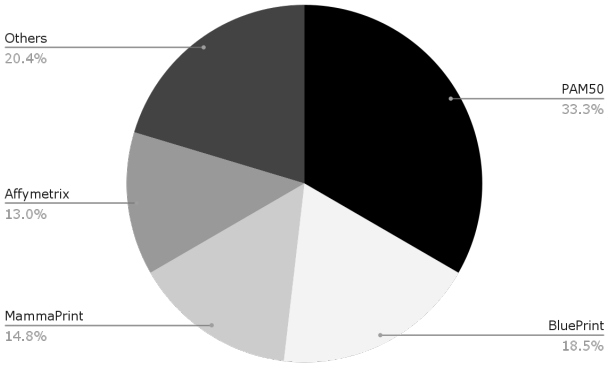

Figure 4: The distribution of different microarray-based platforms for breast cancer subtyping investigated in the included studies (n=45). For studies that included more than one platform, each platform was counted as one (total of 54 counts). The articles included in this review mainly utilized PAM50 technology (n=18/54, 33.3%) in subtyping breast cancer.

Concordance of Microarray-Based Technology with IHC/FISH

Of the 45 included articles, 40 articles reported concordance rates between microarray methods and IHC/FISH (Table 2). The earliest BluePrint/MammaPrint study in the USA reported concordance rates as high as 94–95%, with MammaPrint classifying all HER2 and basal-type tumors as high risk (Nguyen *et al.* 2012, Nunes *et al.* 2016). A more recent publication, however, showed that up to 18% of luminal tumors in the same population are reclassified to basal type by the technology (Whitworth *et al.* 2017). Lower concordance rates that ranged from 65.3% to 76.6% were seen in studies published in the European area, with 30% of tumors having differed classifications using RNA-based methods (Slembrouck *et al. 2019, Viale et al.* 2018, Wuerstlein *et al.* 2019). Notably, in a study investigating 256 early-stage breast cancer patients scheduled for neoadjuvant chemotherapy, 5% of ER+HER2- tumors on IHC were basal type on BluePrint, and 5% of basal type were also reclassified as luminal (Goker *et al.* 2022). Moreover, among HER2+ tumors, a total of 37% of patients were reclassified by microarray as follows: 10% as luminal A, 22% as luminal B, and 5% as basal type. In another study that explored HER2 equivocal tumors on FISH, BluePrint testing classified them as HER2 negative (Bai *et al.* 2023).

Highest concordance rates of up to 100% were reported for TargetPrint technology, especially when discordant cases were retested for IHC/FISH (Grant *et al.* 2015). In a study done in the USA, concordance between IHC and TargetPrint was 93% for ER and 83% for PR (Roepman *et al.* 2009). In another study done in Germany, the concordances of ER, PR, and HER2 were 97%, 86%, and 94% respectively (Gevensleben 2010). A multicenter study showed similar findings of 95% concordance for ER, 80% for PR, and 94% for HER2 (Wesseling *et al.* 2016). For ER status, 82% concordance was seen in IHC, TargetPrint, and BluePrint, but BluePrint was more concordant with TargetPrint than with IHC (Bai *et al.* 2023, Wesseling *et al.* 2016).

Among the different technologies, PAM50 (18/54, 33.3%) had the highest number of publications and investigated populations across different continents (Figure 2 and Figure 4). PAM50, however, reported the lowest concordance rates of 54% and 60% as reported in two studies in South American countries and Sweden (Llera *et al*. 2022, Lundgren *et al*. 2022). Other studies also reported overall discordance ranging from 38.4–40.47%, with one study reporting that IHC/FISH misclassified all basal-like tumors (Dank *et al*. 2023, Erber *et al*. 2022, Kim *et al*. 2019). Distributions of the subtypes varied widely when comparing IHC and PAM50 (Dix-Peek *et al*. 2023, Ohara *et al*. 2019). Poor-to-fair correlation was seen between PAM50 and IHC/FISH when testing for ER, PR, and HER2 (kappa of 0.34, 0.27, and 0.37, respectively), with 5–11% of luminal B tumors classified as luminal A, and 18–36% of luminal A tumors classified as luminal B (Lopez-Tarruella *et al*. 2024). In a cohort of males with breast cancer, half of luminal A tumors on IHC were classified differently by PAM50 (Sanchez-Munoz *et al*. 2018). Concordance improved from poor/moderate (kappa = 0.36–0.57, accuracy = 0.54–0.75) to good (kappa = 0.71–0.69, accuracy = 0.90–0.91) when luminal A and B were collapsed into one group (Holm *et al*. 2021). Improved consistency with clinical subtyping in classifying luminal tumors was also seen when principal component analysis was added to PAM50 results (Raj-Kumar *et al*. 2019). Despite these numerous reports of high discordance, some publications nonetheless reported modest or substantial association (Jenkins *et al*. 2014, Liu *et al*. 2016, Romero *et al*. 2014).

Notably, there were some studies that used PAM50 as the gold standard. The IHC sensitivity and specificity were 33% and 96%, respectively, when classifying luminal A tumors. When classifying luminal B tumors, the sensitivity and specificity were 95% and 41%, respectively (Christensen, Lautrup, Lyng, Moller & Jylling 2020). On the other hand, another reported that the accuracy of IHC was 73% for luminal A, 79% for luminal B, and 88% for basal-like tumors (Allott *et al*. 2018).

Three publications compared Affymetrix with IHC/FISH (Fumagalli *et al*. 2014, Fakri *et al*. 2018, Rossing *et al*. 2018). Very strong correlations were seen for ER and PR with Spearman correlation coefficients of 0.84 and 0.85, respectively. Good correlation, with a Spearman correlation coefficient of 0.70, was also seen for HER2 (Fumagalli *et al*. 2014). Concordance with IHC was 97.5% for ER, 86.4% for PR, and 97.5% for HER2 (Fakhri *et al*. 2018). High overlaps are seen between IHC and Affymetrix in detecting hormone receptor status, but the correlation in HER2 was less (Rossing *et al*. 2018).

Five more microarray technologies explored the utility of microarray methods for breast cancer subtyping. The in-house custom multi-signature array (MSA) showed 90% concordance for ER and 76% for HER2 (Tan *et al*. 2008). The MapQuant assay, on the other hand, had high concordance rates of 97.5% for ER, 91.4% for PR, and 99.3% for HER2 (Moutter *et al*. 2016). The HumanHT012 v4 Expression BeadChips (Illumina) reported substantial agreement (kappa = 0.75) with IHC, with 83% of samples classified similarly by both methods (De Kruijf *et al*. 2014). Another in-house 35k Operon microarray reported an overall concordance of 87%, which increased up to 97% when removing the HER2+ groups (De Ronde *et al*. 2010). Finally, the agreement between the CC Microarray and IHC was 69% (Tramm *et al*. 2014).

Table 2: Concordance of Microarray-Based Technology with IHC/FISH on the molecular subtyping of breast cancer.

	Authors and Year Published	Country	Age	Breast Cancer Stage	Population	n	Microarray Method[a]	IHC/FISH - Microarray Concordance[b]
1	Krijgsman *et al.*, 2012	The Netherlands	≥ or < 50 compared	I-IV; AJCC Cancer Staging edition not reported	patient specimens of breast cancer patients from six different hospitals	1,212	BluePrint, TargetPrint	BluePrint ● TNBC: 43% TargetPrint ● TNBC: 85%
2	Nguyen *et al.*, 2012	USA	35-97	Tx, T1-4, Nx, N0-3; M, not reported; AJCC Cancer Staging edition not reported	patients with a tumor size ≤5 cm, up to three positive lymph nodes, and stage T1-4, N0-3	132	Blueprint, TargetPrint, MammaPrint	Blueprint ● Luminal: 94% ● HER2: 95% ● TNBC: 94% Target Print ● ER: 97% ● PR: 80% ● HER2: 95% MammaPrint & Ki67 ● Luminal A & B substratification: 68%

3	Nunes *et al.*, 2016	USA	22-98	I-III; AJCC Cancer Staging edition not reported	patients self-reported as black or African-American, with early or locally advanced breast cancer	113	MammaPrin, BluePrint, and TargetPrint	BluepPrint ● TNBC → basal, 86% ● ER+ → luminal, 92% ● HER2+ → HER2, 53% TargetPrint ● ER+: 85% ● HER2+: 53% MammaPrint ● HER2+ → high risk, 100% ● Basal → high risk, 100%
4	Whitworth *et al.*, 2017	USA	22-88	T1-4, node positive; AJCC Cancer Staging edition not reported	HR+/HER2- (clinical luminal) tumors from breast cancer patients who had started or were scheduled to start NCT or neoadjuvant hormone therapy.	474	MammaPrint/ BluePrint	HR+/HER2- (clinical luminal) → basal, 18%
5	Viale *et al.*, 2018	The Netherlands, Belgium, France, Germany, Italy, Portugal, Spain, Sweden, United Kingdom (MINDACT Trial)	18-70	T1-T2, operable T3; 0-3 positive nodes; M0; AJCC Cancer Staging edition not reported	female patients with histologically proven operable invasive breast cancer and 0–3 positive lymph nodes	5,806	MammaPrint/BluePrint	Overall concordance, 70% ● Luminal B → luminal A, 54% ● TNBC → luminal, 5% ● HER2+ → luminal, 38% ● HER2+ → basal, 5%

6	Slembrouck *et al*., 2019	France, Belgium	30-91	Primary operable and unilateral breast cancer <3 positive lymph nodes; stage not reported; AJCC Cancer Staging edition not reported	women between 30 and 91 years old with primary operable breast cancer	124	BluePrint/ MammaPrint	Overall concordance, 71.8%-76.6%
7	Wuerstlein *et al*., 2019	Switzerland	≥18 (33-88)	pT1-3, pN0-1, AJCC Cancer Staging edition not reported	female patients 18 years and older with histologically proven pT1-3, pN0-1, HR positive, HER2-negative early breast cancer	452	BluePrint/ MammaPrint	Overall concordance, 65.3%
8	Göker *et al*., 2022	Italy and the Netherlands	≥18 (22-86)	Early stage, T1-4, N0-3, Nx, M0; AJCC Cancer Staging edition not reported	patients more 18 years and older diagnosed with early-stage breast cancer, and started or scheduled to start neoadjuvant systemic therapy	256	BluePrint/ MammaPrint	91% overall concordance ● ER+/HER2- →basal or HER2+, 5% ● HER2+ → luminal A, 10%; luminal B, 22%; basal, 5% ● TNBC → luminal B, 5%
9	Bai *et al.*, 2023	China	26-72	pN0-1 (0–3 positive nodes); AJCC Cancer Staging, 8th ed	breast cancer tissues with HER2>/=4.0 and <6.0, positive hormone receptor by IHC, core needle biopsy specimens prior to neoadjuvant chemotherapy	40	BluePrint, MammaPrint, 21-gene expression assay	HER2+ (HER2 ≥ 4, < 6.0) ● HER2/CEP17 ratio ≥ 2) → HER2-, 100% ● HER2/CEP17 ratio < 2) → HER2-, 100%

10	Roepman *et al*., 2009	The Netherlands	Cohort 1: <53 Cohort 2/3: <61	Cohort 1: I-II; Cohort 2/3: T1–4N0M0; AJCC Cancer Staging edition not reported	patients with confirmed invasive ductal carcinoma or invasive lobular carcinoma and the presence of sufficient tumor cells	636	TargetPrint	TargetPrint ● ER+: 93% ● PR+: 53% ● HER2+ → HER2-, 9%
11	Gevensleben *et al*., 2010	Germany	>36 (n=2), 36-45 (n=16), 46-55 (n=29), >55 (n=93)	I-IIIb; AJCC Cancer Staging edition not reported	patients diagnosed with breast cancer	170	TargetPrint	TargetPrint ER+: 97% PR+: 86% HER2+: 94%
12	Grant *et al*., 2015	South Africa	Mean = 53.1	Early stage; actual stage not reported; AJCC Cancer Staging edition not reported	South African breast cancer patients with tumors that were successfully analysed using MammaPrint microarray profiler	138	TargetPrint	Targetprint Overall concordance, 97% ● after reflex/repeat testing, 100%
13	Wesseling *et al.,* 2016	Italy, Belgium, the Netherlands, New Zealand, Japan, USA	23-98	I-IV; AJCC Cancer Staging edition not reported	patients diagnosed with breast cancer stage I–IV who had a successful TargetPrint test	806	TargetPrint	TargetPrint Overall Concordance ● ER+: 95% ● PR+: 81% ● HER2+: 94% IHC/FISH Inter-hospital Concordance ● ER+: 88-100% ● PR+: 50-100% ● HER2+: 90-100%

14	Grant *et al*., 2019	South Africa	Not reported	Early stage; actual stage not reported; AJCC Cancer Staging edition not reported	records of all patients referred for MammaPrint	128	BluePrint, Target Print	BluePrint ● ER+: 82% ● PR+: 82% TargetPrint ● ER+: 82% ● PR+: 82%
15	Fumagalli *et al*., 2014	Belgium	Not reported	Not reported	patients treated in the institution whose samples are stored in the biorepository	57	Affymetrix	Affymetrix (Spearman Correlation Coefficient) ● ER+: $\rho = 0.84$ ● PR+: $\rho = 0.85$ HER2+: $\rho = 0.70$
16	Falato *et al*., 2016	Sweden	<50 or ≥50	I-III primary breast cancer, AJCC Cancer Staging edition not reported	patients diagnosed and treated for primary breast cancer and subsequent systemic relapse at	220	PAM50	Overall concordance, 64%
17	Rossing *et al*., 2018	Denmark	<50 or ≥50	I-III; AJCC Cancer Staging edition not reported	female breast cancer patients (Stage I–III)	508	Affymetrix	ER+: 91% HER2+: 59%
18	Fakhri *et al*., 2018	Lebanon	29-84	I-IV; AJCC Cancer Staging edition not reported	fresh tissue specimens were collected from females who were newly diagnosed with stage I, II, or III breast cancer	81	Affymetrix	ER+: 97.5% PR+: 86.4% HER2+: 97.5%

19	Tan *et al*., 2008	Singapore	30-87	T1-4; N0 or positive; M0; AJCC Cancert Staging, 6th ed	newly diagnosed nonmetastatic cancer with no prior treatment with histologic diagnosis of invasive ductal carcinoma	165	In-house custom MSA	ER+: 90% HER2+: 76%
20	de Ronde *et al*., 2010	The Netherlands	Mean age: 46 ± 9	T≤2cm or T>2cm, Nx, N0 or node-positive, M, not reported; AJCC Cancer Staging edition not reported	women who received neoadjuvant treatment, eligible for preoperative chemotherapy, diagnosed with invasive breast cancer and either a tumor diameter of at least 3 cm, lymph node involvement or both	195	dye-swap to in-house printed 35 k Operon microarrays	HER2+: 87%-97%
21	de Kruijf *et al*., 2014	The Netherlands	<65 or ≥65	T1-4, N0-3, M0, AJCC Cancer Staging edition not reported	non-metastasized breast cancer patients primarily treated with surgery	822	HumanHT-12 v4 Expression BeadChips (Illumina)	Overall concordance, 83%
22	Tramm *et al*., 2014	Denmark	<70	II-III; AJCC Cancer Staging edition not reported	high-risk breast cancer patients (<70 years old) previously treated with mastectomy and partial axillary dissection	191	Applied Biosystem Human Genome Survey Microarray v2.0 (CC) and PAM50	Applied Biosystem Human Genome Survey Microarray v2.0 (CC): 69% PAM50: 47%

23	Mouttet *et al*., 2016	France	26-70	T1-T2 pN0; AJCC Cancer Staging edition not reported	breast cancer patients with absent pathologic axillary lymph node involvement, a follow up above 10 years, and no neoadjuvant therapy before surgery	163	MapQuant Assay	ER+: 97.5% PR+: 91.4% HER2+: 99.3%
24	Jenkins *et al*., 2014	USA	21-93	T0/T1 vs. ≥T2, node (-) vs (+), M0; AJCC Cancer Staging edition not reported	data of patients from publicly available clinical and gene expression microarray data sets	3,947	PAM50	TNBC → basal-like, 76%
25	Romero *et al*., 2014	Spain	18-78	IIB, IIIA, or IIIB; AJCC Cancer Staging edition not reported	women aged between 18 and 78 years; clinical stage IIB, IIIA, or IIIB breast cancer; and palpable breast tumors not amenable to breast-preserving surgery;	94	PAM50	Overall concordance, 68%
26	Liu *et al*., 2016	USA	Median IQR = 50 (43,57)	Tx, T>2cm, T≤ 2cm; node positive; AJCC Cancer Staging edition not reported	patients with histopathology samples confirming breast cancer and had formalin fixed paraffin embedded tissue samples	1652	PAM50	Distribution of PAM50 subtypes ● Luminal A: 32% ● Luminal B: 26% ● HER2-enriched: 20% ● Basal-like: 22%
27	Allott *et al*., 2018	USA	20-75	I-IV; AJCC staging not reported	African American women	1,381	PAM50	Luminal A: 73% Luminal B: 79% Basal-like: 88%

28	Sánchez-Muñoz *et al*., 2018	Spain	23-92, male	I-IV; AJCC Cancer Staging edition not reported	consenting men with biopsy-confirmed invasive male breast cancer	67	PAM50	Distribution of Molecular Subtypes according to PAM50 signature ● Luminal A: 30% ● Luminal B: 60% ● Basal-like: 0% ● HER2-enriched: 10% Distribution of Molecular Subtypes based on IHC surrogate markers ● Luminal A: 44% ● Luminal B: 51% ● TNBC: ● HER2+ (non-luminal): 1%
29	Bonnefoi *et al*., 2019	France, Switzerland, Netherland, Portugal, Belgium, Poland, Slovenia, Sweden, UK (intergroup multicentre phase III trial)	<70	T4a-d, any N, M0; Any T, N2 or N3, M0; Large operable T2 or T3 tumors; AJCC Cancer Staging edition not reported	Breast cancer patients with locally advanced/ inflammatory or large operable breast cancer prospectively randomised to a taxane versus a non-taxane regimen	60	GEA	Molecular apocrine: 88.3%
30	Raj-Kumar *et al*., 2019	USA	Not reported	Not reported	Patients with primary breast tumors	1,097	PCA-PAM50	Intrinsic Subtype: Conventional vs Refined ● In-house RNA-Seq data set: 60.2% vs 66.1% ● TCGA RNA-Seq data set: 50.98% vs 60.25% ● METABRIC discovery data set: 57.22% agree vs 65.92%

31	Ohara *et al*., 2019	Japan	24-74	T1-4, N0-3; M, not specified; AJCC Cancer Staging edition not reported	Female patients diagnosed with breast cancer who underwent neoadjuvant chemotherapy and surgery (mastectomy or breast conservation surgery) between 2004-2013. Tissue samples were taken prior to neoadjuvant chemotherapy and surgical specimens obtained during surgery	156	PAM50	IHC-Luminal A →PAM50 ● Luminal A: 73% ● Luminal B: 16.2% ● Basal-like: 8.1% ● HER2-enriched: 2.7% IHC-Luminal B →PAM50 ● Luminal A: 33.9% ● Luminal B: 33.9% ● Basal-like: 21.4% ● HER2-enriched: 10.7% IHC-Luminal HER2+ → PAM50 ● Luminal A: 19.4% ● Luminal B: 22.6% ● Basal-like: 3.2% ● HER2-enriched: 54.8%

32	Kim *et al*., 2019	South Korea	21-78	Stage I-IV, AJCC Cancer Staging edition not reported	Premenopausal and postmenopausal asian women with tissue diagnosis of breast cancer with stages ranging from I to IV, and with hormone receptor and HER2 status	605	PAM50	PAM50 overall concordance: 61.6% IHC-Luminal A → PAM50 ● HER2-enriched: 4% ● TNBC: 6% IHC-HER2-enriched →PAM50 ● Luminal A: 4% ● Luminal B: 6% ● TNBC: 9% IHC-TNBC-enriched → PAM50 ● Luminal A: 2% ● HER2-enriched: 13%
33	Christensen *et al*., 2020	Denmark	40-92, male	T0/T1 vs. ≥T2; Nx, N0, N+ (node classification, not reported); M, not reported; AJCC Cancer Staging edition not reported	FFPE tumor samples from men receiving surgical treatment for male breast cancer with enough tumor tissue remaining from pre-treatment biopsies	37	PAM50	Distribution of Molecular Subtypes according to PAM50 signature ● Luminal A: 39% ● Luminal B: 56% ● Basal-like: 5% ● HER2-enriched: 0% Distribution of Molecular Subtypes based on IHC surrogate markers ● Luminal A-like: 15% ● Luminal B-like: 80% ● Basal-like: 5% ● HER2+ (non-luminal): 0%

34	Holm *et al*., 2021	Sweden	28-79	< or ≥T2, node-negative or node-positive; AJCC Cancer Staging edition not reported	diagnosed breast cancer tumors with Ki-67 availability and complete information in all markers	798	PAM50	kappa = 0.36-0.57
35	Erber *et al*., 2022	Germany	39-78	I-II; T not stated, node negative, node positive (1-3 nodes); AJCC Cancer Staging edition not reported	diagnosed invasive breast cancer patients	142	PAM50	Overall PAM50 concordance: 61.6% IHC-Luminal A →PAM50 ● Luminal A: 82.5% ● Luminal B: 17.5% IHC-Luminal B →PAM50 ● Luminal A: 58.9% ● Luminal B: 41.1%
36	Llera *et al*., 2022	Argentina, Brazil, Chile, Mexico, Uruguay	≥18	II-III; AJCC Cancer Staging, 7th edition	Latin American woman of any ethnicity residing in the recruitment countries, aged 18 years or older, with AJCC 7 clinical stage II and III breast cancer, with ECOG performance status 0-1, accessible for biopsy or candidate for primary surgery	1,071	PAM50	Overall PAM50 concordance: 60% TNBC: 73%
37	Lundgren *et al*., 2022	Sweden	≥18	II; AJCC Cancer Staging edition not reported	premenopausal women between 2 years of adjuvant tamoxifen or no systemic treatment	564	PAM50	Overall PAM50 concordance: 54% ● Luminal A: 91% ● Luminal B: 42%

38	Dank *et al.*, 2023	Hungary	≥18	I-IV; TNM Stage, T1-4, N0-3, M0-1; AJCC Cancer Staging 8th edition		42	PAM50	Overall PAM50 concordance: 60%
39	Lopez-Tarruella *et al.*, 2023	Spain	22-85	T0/T1 vs. ≥T2; N0, node-positive (1-3 nodes), M, not stated; AJCC Cancer Staging edition not reported	tumor samples referred for PAM50 testing with positive hormone receptors and positive HER2	1,028	PAM50	Proxy 1, 2 and 3 ● Luminal A: 38%, 30%, and 49% ● Luminal B: 28%, 30%, and 22%
40	Dix-Peek *et al.*, 2023	South Africa	≥18	Stage I-IV, T1-4, N0-3, M0-1; AJCC Cancer Staging, 8th edition	discordance between PAM50 intrinsic subtyping and immunohistochemistry in South African women with breast cancer	378	PAM50	Distribution of Tumors (IHC vs PAM-50) ● Luminal A: 6.9% vs. 19.3% ● Luminal B: 72.7% vs 32.5% ● HER2+: 5.31 vs 23.5% ● Basal-like: 15.11 vs 24.6%

In this review, it was noted that PAM50 technology had the most publications but had the lowest concordance rates compared to IHC/FISH. Some potential reasons why PAM50 had lower concordance rates compared to other technologies include: (1) variation in genetic signatures; (2) tumor heterogeneity sensitivity; and (3) subtype classification differences. First, differences in genetic signatures used may potentially explain why the PAM50, a 50-gene signature, may detect more genetic variations compared to IHC/FISH, translating to higher discordance rates (Parker *et al*. 2009, Piccart *et al*. 2012). Second, PAM50 could potentially be more sensitive in detecting a heterogeneous tumor sample, particularly those breast cancer tissues with differential responses to treatment, which may be characterized at the molecular level (Chang *et al*. 2023). Third, subtype classification differences may contribute to lower concordance rates as IHC/FISH classify tumors based on the protein expression compared to PAM50, which classify them based on mRNA expression. This inherent difference in how they detect biomarkers for breast cancer molecular subtyping can greatly impact the concordance rates (Piccart *et al.* 2012, Chang *et al*. 2023).

Although this trend of lower concordance rates relative to IHC/FISH had been observed, some studies even used PAM50 technology as their gold standard for breast cancer molecular subtyping (Christensen *et al.* 2020). We surmised that the innate advantages of PAM50 can possibly explain why PAM50, instead of the traditional IHC/FISH, has been utilized by some studies as their gold standard (Cardoso *et al.,* 2016, Sparano *et al.,* 2018). In the MINDACT trial, Cardoso *et al.* (2016) highlighted improved risk stratification and prognosis, which was management-changing. Additionally, the TAILORx Trial also impacted the management of patients, particularly in determining whether chemotherapy will be administered, because PAM50 effectively subtyped them into patients with low or high risk of recurrence (Sparano *et al.* 2018). Recently, studies in both the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO), presented the growing use of PAM50 in breast cancer molecular subtyping and its promising utility not only for research but ultimately for clinical decision making, thereby promoting more personalized treatment approaches (Sifakis *et al.,* 2024). Furthermore, in one study included in our paper, PAM50 together with PCA improved consistency between breast cancer intrinsic and clinical subtyping (Raj-Kumar *et al.* 2019). Integrating PCA to PAM50 through the PCA-PAM50 R package provided a tool to improve data handling across different and complex data sets. Overall, PAM50 has been increasingly utilized in breast cancer molecular subtyping, and major societies are currently validating its use as one of the parameters for eventual recommendations on clinical practice guidelines.

Microarray tests classified luminal tumors, which showed better overall DMFS compared to those obtained through IHC. Approximately 5% of luminal tumors were reclassified between luminal and basal types(Goker *et al.* 2022). In a retrospective cohort study on HER2-enriched tumors that received neoadjuvant chemotherapy, 32% were reclassified to luminal subtypes by microarray. Those HER2 equivocal by FISH were reclassified by microarray into HER2-negative (Bai *et al.* 2023). These findings support the clinical utility of microarray-based testing, as those luminal subtypes could have proceeded with excision, then adjuvant chemotherapy, and foregone adjuvant targeted therapy. Certainly, the most important role of breast cancer molecular subtyping is to guide the management, particularly in hormonal therapy, neoadjuvant/adjuvant chemotherapy, radiotherapy, and/or surgery. In this study, we noted that microarray-based methods were able to identify patients who may need neoadjuvant treatment. For instance, BluePrint/MammaPrint can classify patients who can benefit from neoadjuvant treatment (Whitworth *et al.* 2017, Krijgman *et al.* 2012, Baron *et al.* 2016). However, Wuerstlein *et al.* (2019) highlighted that only 14–15.1% of medical oncologists changed their decisions from not giving to giving chemotherapy and vice versa. The primary reason could be the lack of recommendations from cancer societies worldwide. It has been stated earlier that most societies are still validating the utility of PAM50. The hesitancy of clinicians to adapt the use of the more comprehensive microarray-based results can also be explained by lack of clinical validation and standardization, clinical experience and familiarity, data complexity and interpretation, turnaround time, cost, accessibility/availability, and regulatory and reimbursement barriers (Dix-Peek *et al.* 2023, Coates *et al.* 2015, Schaibley *et al.* 2022, Mathews *et al.* 2019, Sireci *et al.* 2020). These challenges may have been more apparent in developing countries, and thus, can potentially affect the survival of breast cancer patients. Hence, the adoption of microarray-based breast cancer molecular subtyping is not only management-changing but may prognosticate the overall survival of breast cancer patients. This is usually measured in clinical studies through distant metastasis-free survival (DMFS) in 5 or 10 years (Goker *et al.* 2022, Krijgsman *et al.* 2012, Ohara *et al.* 2019).

With the current advancements in breast cancer studies, microarray-based genomic profiling tests such as MammaPrint and Blueprint are available for breast cancer subtype classification, and these tests can also predict the risk of distant recurrence for a certain subset with high-risk clinical features. Patients with high-risk features but who had low genomic risk and did not undergo adjuvant chemotherapy had a 5-year rate of survival with distant metastasis of 94.7%. The MINDACT study above concluded that 46% of clinically defined high-risk patients may not forgo adjuvant chemotherapy (Cardoso *et al.* 2016).

Prognostic Value of Microarray on Treatment Response

The main role of breast cancer subtyping is to guide management, such as recommending the need for hormonal therapy, neoadjuvant/adjuvant chemotherapy, radiotherapy, or outright surgery. Hence, molecular subtyping methods should be able to closely predict which patients would respond to certain regimens and benefit later with better survival. We further evaluated the ability of the abovementioned microarray-based technologies to provide a prognosis on certain treatment regimens. Notably, BluePrint reclassified patients who were more responsive to neoadjuvant chemotherapy to the HER2 and basal type, while less responsive patients were reassigned to the luminal type (Goker *et al*. 2022). In three studies that examined patients who received neoadjuvant chemotherapy, significantly lower pCR rates were observed among those classified by BluePrint/MammaPrint under the luminal subtype compared with HER2 and basal subtypes that presented with higher pCR after neoadjuvant chemotherapy (Whitworth *et al*. 2017, Krijgsman *et al*. 2012, Baron *et al*. 2016). PCRs were as low as 6.1% and 8.7% for luminal A and B, respectively, compared to 55% in HER2 and 37.1% in basal tumors (Baron *et al*. 2016). This implies that BluePrint may distinguish which patients would benefit from neoadjuvant treatment.

Of particular interest were the breast cancer patients with equivocal HER2 on FISH (>4.0 and <6.0), but classified as high-risk on MammaPrint, who achieved pCR after treatment with trastuzumab or pertuzumab (Bai *et al*. 2023). Among HER2-positive patients classified by BluePrint, the pCR was 71.9% among those given pertuzumab versus 43.5% among those who did not receive the drug (Liefaard *et al*. 2023). Up to 14% of physicians switched decisions from managing with chemotherapy to without chemotherapy, and conversely, 15.1% switched from without chemotherapy to with chemotherapy, after MammaPrint results (Wuerstlein *et al*. 2019).

Similar findings were seen in papers examining the prognostic value of PAM50. Higher pCR was also seen among patients classified by PAM50 with non-luminal types regardless of IHC profiles (Falato *et al*. 2016, Jensen *et al*. 2023). In two studies that examined patients treated with tamoxifen, IHC/FISH was not able to provide a discernible difference in the prognosis of luminal A and B tumors with tamoxifen treatment (Holm *et al*. 2021, Lundgren *et al*. 2022). It was only when PAM50 signatures were used that luminal A tumors showed higher response rates to tamoxifen compared to luminal B tumors (Sanchez-Muñoz *et al*. 2018). Luminal A tumors classified by PAM50 showed benefit with adjuvant tamoxifen, while luminal B tumors classified similarly by both PAM50 and IHC showed poor prognosis (Lundgren *et al*. 2022). Those that were luminal B in IHC but reclassified as luminal A on PAM50, on the other hand, showed better prognosis. In a study enrolling women with HER2-positive breast cancer, five out of eight PAM50 signatures were found to be associated with pCR after trastuzumab-based neoadjuvant chemotherapy: (1) HER2-enriched, (2) ROR-S, (3) ROR-P, (4) basal-like, and (5) proliferation scores (Pernas *et al*. 2019). Based on these studies, PAM50 generally provides benefits in distinguishing between luminal A and B tumors (Jensen *et al*. 2023, Pernas *et al*. 2019, Falata *et al*. 2016, Krijgsman *et al*. 2012, Lundgren *et al*. 2022).

Prognostic Value of Microarray on Patient Survival

Molecular biomarkers are also useful to prognosticate patients to better or worse survival outcomes. Hence, some studies also explored the prognostic value of microarray on survival of breast cancer patients.

Among triple-negative early breast cancer patients, BluePrint was able to reclassify 5% of tumors to the luminal subtype, with a 5-year distant metastasis-free survival (DMFS) rate of 100% which was higher than the molecularly subtyped HER2+ and basal type (Viale *et al*. 2018). In another study, patients with BluePrint-classified luminal tumors showed better overall DMFS, but those with basal-type tumors showed similar prognosis whether defined by IHC/FISH or BluePrint (Goker *et al*. 2022). In contrast, one study did not see a significant association of the BluePrint subtypes with overall survival (OS) for an average follow-up of 6.9 years (Liefaard *et al*. 2023).

PAM50 has also been shown to provide more prognostic information on OS compared to pathology-based methods (Liu *et al*. 2016, Romero *et al*. 2014, Christensen *et al*. 2020). Patients with PAM50-classified luminal A tumors had the best outcome, those with basal-like tumors had the worst prognosis and luminal B tumors had intermediate survival. Unfortunately, IHC was only able to discriminate outcomes between TNBC and the others (Llera *et al*. 2022). An investigation on male breast cancer patients showed that PAM50 luminal B tumors had significantly worse OS than luminal A tumors, a pattern that was not seen on IHC (Christensen *et al*. 2020). In another study, substantial agreement on 10-year survival was seen for IHC and PAM50 HER2 and basal-like tumors, but different trends were seen for the luminal subtypes (Holm *et al*. 2021). Patients with PAM50 luminal A tumors treated with adjuvant hormonal therapy have a better prognosis compared with other subtypes (Ohara *et al*. 2019, Wang *et al*. 2021). With tamoxifen treatment, PAM50 luminal A tumors exhibited higher overall survival rates compared to PAM50 luminal B tumors (Lundgren *et al*. 2022). Contrasting results, however, were seen in two studies showing no significant differences in luminal A and B tumors (Sanchez-Muñoz *et al*. 2018) and lower survival rates in hormone-positive tumors (Dank *et al*. 2023).

There were some studies that explored a change in survival or remission in patients whose breast cancer was classified with microarray-based methods, leading to a change in a treatment regimen. In the MINDACT trials, early-stage breast cancer patients were subtyped with MammaPrint, and patients classified as low genomic risk were de-escalated to not receiving adjuvant chemotherapy. Results showed non-inferiority in 5-year DMFS in the group where adjuvant chemotherapy (94.70%) was withheld compared to the standard adjuvant chemotherapy regimen group (95.9%) (Cardoso *et al.* 2016). In their follow-up study, similar non-inferiority findings were obtained in terms of the 8-year DMFS (92.0% vs. 93.6%) and 8-year OS (95.7% vs. 96.0%) (Piccart *et al.* 2012, Piccart *et al*. 2021). Overall, both MINDACT trials had approximately a 46% reduction in chemotherapy use and a subsequent decrease in long-term toxicity (Cardoso *et al.* 2016, Piccart *et al.* 2021). Based on the results of these landmark trials, it has now been adopted by the National Comprehensive Cancer Network guidelines (NCCN) (version 5.2025) with a level 1 category of evidence and consensus in the use of MammaPrint for consideration of adjuvant systemic therapy in pN0 and pN1 (1-3 positive nodes).

Recently, newer studies, which determined the ability of microarray-based technologies in the investigation of breast cancer recurrence prediction (i.e., EndoPredict®), DNA methylation for subtype classification, and validation of immune-related 23 (IRSN-23) gene signature for neoadjuvant chemotherapy (Watanabe *et al.* 2024, Sota *et al.* 2025, Panigoro *et al.* 2025). However, these recent studies did not explicitly investigate the concordance of IHC/FISH with microarray. While they used IHC/FISH for initial classification of breast cancer subtypes, there were no reported percent agreements or computed kappa statistics between IHC/FISH and microarray. The multigene EndoPredict® assay classified the low-risk ER+/HER2- (luminal) subtype as having a 5-year distant recurrence-free survival of 95.2% (Watanabe *et al.* 2024). Another study utilized microarray to methylation-specific polymerase chain reaction (MSP) and was translated for DNA methylation profiling, which was shown to be useful in the breast cancer subtype classifications. In this study, they developed MSP assays, which resulted from the identification of subtype-specific methylation patterns with accuracies of 75% and 76% for luminal A and B, respectively (Panigoro *et al.* 2025). In combination with the PAM-50 intrinsic subtype classifier, the IRSN-23 gene signature can further categorize patients undergoing neoadjuvant chemotherapy into chemoresistant and chemosensitive groups. The IRSN-23-classified chemosensitive had a higher pCR rate compared to the non-sensitive groups (Sota *et al.* 2025). Notably, integration of MRI radiomics and microarray gene expression analysis has also been studied recently in their role to predict pCR in breast cancer patients undergoing NAT. They compared three different machine learning models: (1) radiomics (MRI) alone; (2) genomics (microarray) alone; and (3) radiogenomics (MRI+microarray). Although the radiogenomics group (AUC = 0.607) had the highest AUC, results showed that there were no significant differences ($p > .05$) when compared to the radiomics alone (AUC = 0.563) and genomics alone (AUC = 0.559) models (Oda *et al.* 2025).

The cost of molecular methods is usually a challenge, especially in low-to-middle income countries (LMICs). Multiple studies, however, have already shown the cost-effectiveness of these procedures as they prevent the costs of unnecessary treatment, especially among those who are misclassified (Rojas *et al.* 2023). While numerous studies have shown the utility of gene-expression-based assays, this review was limited only to microarray-based technologies. Other RNA-based assays, such as Oncotype Dx, have also shown utility in the clinical setting, but are polymerase chain reaction-based (Lashen, Toss, Fadhil, Oni, Madhusudan & Rakha, 2023). This review was also limited to articles in the English language and indexed in selected databases. Moreover, while the studies included in the paper involved multiple countries, these studies did not necessarily come from an equal distribution of

regions. While we are able to report on the concordance and utility of these new technologies, the applicability of these methods in various races may be limited due to variations in the genetics of certain populations. Variations in patient characteristics could not be controlled in this review. Data on treatment response and survival were also limited to only selected regimens in the included studies and may not necessarily be representative of the wide array of treatment regimens in breast cancer management, especially of the newer drugs. Follow-up durations were also variable among the different studies. Finally, a formal risk-of-bias assessment was not performed due to the exploratory nature of the review. Instead, pertinent results of all the included studies were discussed and described.

Further studies may help elucidate the applicability and cost-effectiveness of microarray methods in the lower-income populations. Moreover, investigations on the genomic profiles of relatively underrepresented groups (e.g., Asia) would help establish novel technologies designed and applied to specific populations. Our study has demonstrated the potential of microarray-based methods in breast cancer diagnosis and management. It may pave the way for further development of these modern techniques for patient care.

CONCLUSION

Our systematic review included 45 articles out of the 1006 articles in our search showed that most microarray-based genomic profiling in the molecular subtyping of breast cancer was done in the US and Europe. There was a variable IHC/FISH concordance rate on the microarray-based genomic profiling in the molecular subtyping of breast cancer. Microarray-based tests showed promising prognostic capability for treatment response and survival, and may be useful to better triage patients who would benefit from certain treatment approaches. Overall, our systematic review showed the potential of microarray-based technologies in improving molecular subtyping of breast cancer and prognosticating treatment response and survival.

ACKNOWLEDGMENTS

The authors would like to thank MD-PhD (Molecular Medicine) program for sponsoring the publication fee and the Department of Science and Technology for deploying Dr. Elgin Paul B. Quebral to the Virology Laboratory, Department of Medical Microbiology, College of Public Health, University of the Philippines Manila under the Career Incentive Program of the the Science Education Institute.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

CONTRIBUTIONS OF INDIVIDUAL AUTHORS

NDS and EPQ: contributed equally in the conceptualization, identification, screening, synthesis and analysis of the studies, writing of the draft and the final manuscript, and supervision in the conduct of the study. EDO: study conceptualization; spearheaded the identification, and screening of studies; manuscript writing. VJ, DKB, KTB and AF: identified, screened and analyzed included studies and helped write the manuscript. AV supervised in data analysis and manuscript writing. SDS: study conceptualization; supervision in the overall conduct of the study; writing of manuscript; approval of manuscript; funding acquisition for publication fee. NDS, EPQ and SDS wrote the original draft and revisions of the manuscript.

REFERENCES

Allott EH, Geradts J, Cohen SM, Khoury T, Zirpoli GR, Bshara W, *et al.* Frequency of breast cancer subtypes among African American women in the AMBER consortium. *Breast Cancer Res* 2018;20:12.

Bai Q, Lv H, Bao L, Yang Y, Zhang X, Chang H, *et al.* Invasive Breast Cancer with HER2 ≥4.0 and.<6.0: : Risk Classification and Molecular Typing by a 21-Gene Expression Assay and MammaPrint Plus BluePrint Testing. *Breast Cancer (Dove Med Press)* 2023;15:563–75.

Baron P, Beitsch P, Boselli D, Symanowski J, Pellicane JV, Beatty J, et al. Impact of Tumor Size on Probability of Pathologic Complete Response After Neoadjuvant Chemotherapy. *Ann Surg Oncol* 2016;23:1522–9.

Bernemann C, Hülsewig C, Ruckert C, Schäfer S, Blümel L, Hempel G, *et al*. Influence of secreted frizzled receptor protein 1 (SFRP1) on neoadjuvant chemotherapy in triple negative breast cancer does not rely on WNT signaling. *Mol Cancer* 2014;13:174.

Bonnefoi H, MacGrogan G, Poncet C, Iggo R, Pommeret F, *et al*. Molecular apocrine tumours in EORTC 10994/BIG 1-00 phase III study: pathological response after neoadjuvant chemotherapy and clinical outcomes. *Br J Cancer* 2019;120:913–21.

Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, *et al*. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024;74:229–63.

Cardoso F, van't Veer LJ, Bogaerts J, Slaets L, Viale G, Delaloge S, *et al*. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. *N Engl J Med*. 2016;375(8):717-729.

Chang YT, Hong ZJ, Yu JC, Lin WZ, Huang TY, Tsai HH, et al. Advancing breast cancer subtyping: optimizing immunohistochemical staining classification with insights from real-world Taiwanese data. *Am J Cancer Res*. 2023;13(11):5719-5732.

Christensen LG, Lautrup MD, Lyng MB, Möller S, Jylling AMB. Subtyping of male breast cancer by PAM50 and immunohistochemistry: a pilot study of a consecutive Danish cohort. *APMIS* 2020;128:523–30.

Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, *et al*. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol*. 2015;26(8):1533-1546.

Curigliano G, Burstein HJ, Gnant M, Loibl S, Cameron D, Regan MM, *et al*. Understanding breast cancer complexity to improve patient outcomes: The St Gallen International Consensus Conference for the Primary Therapy of Individuals with Early Breast Cancer 2023. *Ann Oncol* 2023;34:970–86.

Dank M, Mühl D, Pölhös A, Csanda R, Herold M, Kovacs AK, *et al*. The Prediction Analysis of Microarray 50 (PAM50) Gene Expression Classifier Utilized in Indeterminate-Risk Breast

Cancer Patients in Hungary: A Consecutive 5-Year Experience. *Genes* 2023;14:1708.

De Kruijf EM, Bastiaannet E, Rubertá F, De Craen AJM, Kuppen PJK, Smit VTHBM, *et al*. Comparison of frequencies and prognostic effect of molecular subtypes between young and elderly breast cancer patients. *Mol Oncol* 2014;8:1014–25.

De Ronde JJ, Hannemann J, Halfwerk H, Mulder L, Straver ME, Vrancken Peeters M-JTFD, *et al*. Concordance of clinical and molecular breast cancer subtyping in the context of preoperative chemotherapy response. *Breast Cancer Res Treat* 2010;119:119–26.

Dix-Peek T, Phakathi BP, Van Den Berg EJ, Dickens C, Augustine TN, Cubasch H, *et al*. Discordance between PAM50 intrinsic subtyping and immunohistochemistry in South African women with breast cancer. *Breast Cancer Res Treat* 2023;199:1–12.

Dowsett M, Sestak I, Lopez-Knowles E, Sidhu K, Dunbier AK, Cowens JW, *et al*. Comparison of PAM50 risk of recurrence score with oncotype DX and IHC4 for predicting risk of distant recurrence after endocrine therapy. *J Clin Oncol* 2013;31:2783–90.

Erber R, Angeloni M, Stöhr R, Lux MP, Ulbrich-Gebauer D, Pelz E, *et al.* Molecular Subtyping of Invasive Breast Cancer Using a PAM50-Based Multigene Expression Test-Comparison with Molecular-Like Subtyping by Tumor Grade/Immunohistochemistry and Influence on Oncologist's Decision on Systemic Therapy in a Real-World Setting. *Int J Mol Sci* 2022;23:8716.

Fakhri GB, Akel RS, Khalil MK, Mukherji DA, Boulos FI, Tfayli AH. Concordance between Immunohistochemistry and Microarray Gene Expression Profiling for Estrogen Receptor, Progesterone Receptor, and HER2 Receptor Statuses in Breast Cancer Patients in Lebanon. *Int J Breast Cancer* 2018;2018:1–6.

Falato C, Tobin NP, Lorent J, Lindström LS, Bergh J, Foukakis T. Intrinsic subtypes and genomic signatures of primary breast cancer and prognosis after systemic relapse. *Mol Oncol* 2016;10:517–25.

Fumagalli D, Blanchet-Cohen A, Brown D, Desmedt C, Gacquer D, Michiels S, *et al.* Transfer of clinically relevant gene expression signatures in breast cancer: from Affymetrix microarray to Illumina RNA-Sequencing technology. *BMC Genomics* 2014;15:1008.

Gevensleben. Comparison of MammaPrint and TargetPrint results with clinical parameters in German patients with early stage breast cancer. *Int J Mol Med* 2010 Oct 21.;26.

Göker E, Hendriks MP, Van Tilburg M, Barcaru A, Mittempergher L, Van Egmond A, *et al.* Treatment response and 5-year distant metastasis-free survival outcome in breast cancer patients after the use of MammaPrint and BluePrint to guide preoperative systemic treatment decisions. *Eur J Cancer* 2022;167:92–102.

Grant KA, Myburgh EJ, Murray E, Pienaar FM, Kidd M, Wright CA, *et al*. Reclassification of early-stage breast cancer into treatment groups by combining the use of immunohistochemistry and microarray analysis. *South Afr J Sci* 2019;115.

Grant KA, Pienaar FM, Brundyn K, Swart G, Gericke GS, Myburgh EJ, *et al.* Incorporating microarray assessment of HER2 status in clinical practice supports individualised therapy in early-stage breast cancer. *The Breast* 2015;24:137–42.

Harbeck N, Thomssen C, Gnant M. St. Gallen 2013: Brief Preliminary Summary of the Consensus Discussion. *Breast Care* 2013;8:102–9.

Holm J, Yu NY-L, Johansson A, Ploner A, Hall P, Lindström LS, et al. Concordance of Immunohistochemistry-Based and Gene Expression-Based Subtyping in Breast Cancer. *JNCI Cancer Spectr* 2021;5:pkaa087.

Jenkins EO, Deal AM, Anders CK, Prat A, Perou CM, Carey LA, *et al.* Age-Specific Changes in Intrinsic Breast Cancer Subtypes: A Focus on Older Women. *The Oncologist* 2014;19:1076–83.

Jensen MB, Pedersen CB, Misiakou MA, Talman MLM, Gibson L, Tange UB, *et al.* Multigene profiles to guide the use of neoadjuvant chemotherapy for breast cancer: a Copenhagen Breast Cancer Genomics Study. *Npj Breast Cancer* 2023;9:47.

Kim HK, Park KH, Kim Y, Park SE, Lee HS, Lim SW, et al. Discordance of the PAM50 Intrinsic Subtypes Compared with Immunohistochemistry-Based Surrogate in Breast Cancer Patients: Potential Implication of Genomic Alterations of Discordance. *Cancer Res Treat* 2019;51:737–47.

Krijgsman O, Roepman P, Zwart W, Carroll JS, Tian S, De Snoo FA, *et al.* A diagnostic gene profile for molecular subtyping of breast cancer associated with treatment response. *Breast Cancer Res Treat* 2012;133:37–47.

Lashen A, Toss MS, Fadhil W, Oni G, Madhusudan S, Rakha E. Evaluation oncotype DX® 21-gene recurrence score and clinicopathological parameters: a single institutional experience. *Histopathology*. 2023;82(5):755-766. doi:10.1111/his.14863.

Lei S, Zheng R, Zhang S, Wang S, Chen R, Sun K, et al. Global patterns of breast cancer incidence and mortality: A population-based cancer registry data analysis from 2000 to 2020. *Cancer Commun* 2021;41:1183–94.

Liefaard MC, Van Der Voort A, Van Ramshorst MS, Sanders J, Vonk S, Horlings HM, *et al.* BluePrint molecular subtypes predict response to neoadjuvant pertuzumab in HER2-positive breast cancer. *Breast Cancer Res* 2023;25:71.

Liu MC, Pitcher BN, Mardis ER, Davies SR, Friedman PN, Snider JE, *et al.* PAM50 gene signatures and breast cancer prognosis with adjuvant anthracycline- and taxane-based chemotherapy: correlative analysis of C9741 (Alliance). *Npj Breast Cancer* 2016;2:15023.

Llera AS, Abdelhay ESFW, Artagaveytia N, Daneri-Navarro A, Müller B, Velazquez C, *et al.* The Transcriptomic Portrait of Locally Advanced Breast Cancer and Its Prognostic Value in a Multi-Country Cohort of Latin American Patients. *Front Oncol* 2022;12:835626.

Lopez-Tarruella S, Del Monte-Millán M, Roche-Molina M, Jerez Y, Echavarria Diaz-Guardamino I, Herrero López B, *et al.* Correlation between breast cancer subtypes determined by immunohistochemistry and n-COUNTER PAM50 assay: a real-world study. *Breast Cancer Res Treat* 2024;203:163–72.

Lundgren C, Bendahl P-O, Church SE, Ekholm M, Fernö M, Forsare C, *et al.* PAM50 subtyping and ROR score add long-term prognostic information in premenopausal breast cancer patients. *Npj Breast Cancer* 2022;8:61.

Mathews JC, Nadeem S, Levine AJ, Pouryahya M, Deasy JO, Tannenbaum A. Robust and interpretable PAM50 reclassification exhibits survival advantage for myoepithelial and immune phenotypes. *NPJ breast cancer*, 2019; 5:30.

Mouttet D, Laé M, Caly M, Gentien D, Carpentier S, Peyro-Saint-Paul H, et al. Estrogen-Receptor, Progesterone-Receptor and HER2 Status Determination in Invasive Breast Cancer. Concordance between Immuno-Histochemistry and MapQuantTM Microarray Based Assay. *PLOS ONE* 2016;11:e0146474.

National Comprehensive Cancer Network. (2025). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Breast Cancer (Version 5.2025). https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Nguyen B, Cusumano PG, Deck K, Kerlin D, Garcia AA, Barone, JL, *et al.* Comparison of Molecular Subtyping with BluePrint, MammaPrint, and TargetPrint to Local Clinical Subtyping in Breast Cancer Patients. *Annals of Surgical Oncology*, 2012; 19(10), 3257–3263.

Nunes RA, Wray L, Mete M, Herbolsheimer P, Smith KL, Bijelic L, *et al.* Genomic profiling of breast cancer in African-American women using MammaPrint. *Breast Cancer Res Treat* 2016;159:481–8.

Oda S, Tokuda Y, Suzuki Y, *et al.* Integrative Radiogenomics Using MRI Radiomics and Microarray Gene Expression Analysis to Predict Pathological Complete Response in Patients with Breast Cancer Undergoing Neoadjuvant Chemotherapy. *Cureus.* 2025;17(6):e86287.

Ohara AM, Naoi Y, Shimazu K, Kagara N, Shimoda M, Tanei T, *et al.* PAM50 for prediction of response to neoadjuvant chemotherapy for ER-positive breast cancer. *Breast Cancer Res Treat* 2019;173:533–43.

Ortega P, Pascual T, Martínez-Sáez O, Hernando C, Servitja S, Fernández-Abad M, *et al.* Development of a multiparametric prognostic score based on PAM50, in patients with HR+/HER2- advanced breast cancer (aBC) treated with endocrine therapy (ET) plus cyclin dependent kinase 4 and 6 inhibitors (CDKi), within the CDK-PREDICT (SOLTI-1801) study and HCB cohort. *J Clin Oncol* 2024;42:1061–1061.

Parker JS, Mullins M, Cheang MCU, Leung S, Voduc D, Vickery T, *et al*. Supervised Risk Predictor of Breast Cancer Based on Intrinsic Subtypes. *J Clin Oncol* 2009;27:1160–7.

Panigoro SS, Paramita RI, Wanandi SI, Fadilah F, Wibisana IG, Sutandyo N. DNA methylation profiles for breast cancer subtype classifications: A translational study from microarray to methylation-specific PCR (MSP). *Narra J*. 2025;5(1):e1364.

Pernas S, Petit A, Climent F, Paré L, Perez-Martin J, Ventura L, *et al*. PAM50 Subtypes in Baseline and Residual Tumors Following Neoadjuvant Trastuzumab-Based Chemotherapy in HER2-Positive Breast Cancer: A Consecutive-Series From a Single Institution. *Front Oncol* 2019;9:707.

Perou CM, Sørlie T, Eisen MB, Van De Rijn M, Jeffrey SS, Rees CA, *et al*. Molecular portraits of human breast tumours. *Nature* 2000;406:747–52.

Piccart M, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Gianni L, *et al*. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*, 2012; 357(1):19-28.

Piccart M, van 't Veer LJ, Poncet C, *et al.* 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. *Lancet Oncol*. 2021;22(4):476-488.

Raj-Kumar P-K, Liu J, Hooke JA, Kovatich AJ, Kvecher L, Shriver CD, *et al.* PCA-PAM50 improves consistency between breast cancer intrinsic and clinical subtyping reclassifying a subset of luminal A tumors as luminal B. *Sci Rep* 2019;9:7956.

Roepman P, Horlings HM, Krijgsman O, Kok M, Bueno-de-Mesquita JM, Bender R, *et al.* Microarray-Based Determination of Estrogen Receptor, Progesterone Receptor, and HER2 Receptor Status in Breast Cancer. *Clin Cancer Res* 2009;15:7003–11.

Rojas L, Rojas-Reyes MX, Rosselli D, Ariza JG, Ruiz-Patiño A, Cardona AF. Cost-utility analysis of genomic profiling in early breast cancer in Colombia. *Cost Eff Resour Alloc* 2023;21:42.

Romero A, Prat A, García-Sáenz JÁ, Del Prado N, Pelayo A, Furió V, *et al.* Assignment of tumor subtype by genomic testing and pathologic-based approximations: implications on patient's management and therapy selection. *Clin Transl Oncol* 2014;16:386–94.

Rossing M, Østrup O, Majewski WW, Kinalis S, Jensen M-B, Knoop A, *et al.* Molecular subtyping of breast cancer improves identification of both high and low risk patients. *Acta Oncol* 2018;57:58–66.

Sanchez-Muñoz A, Vicioso L, Santonja A, Álvarez M, Plata-Fernández Y, Miramón J, *et al.* Male breast cancer: correlation between immunohistochemical subtyping and PAM50 intrinsic subtypes, and the subsequent clinical outcomes. *Mod Pathol* 2018;31:299–306.

Sarhadi S, Armani A, Jafari-Gharabaghlou D, Sadeghi S, & Zarghami, N. Cross-platform gene expression profiling of breast cancer: Exploring the relationship between breast cancer grades and gene expression pattern. *Heliyon* 2024; 10(8), e29736.

Schaibley VM, Ramos IN, Woosley RL, Curry S, Hays S & Ramos KS. Limited Genomics Training Among Physicians Remains a Barrier to Genomics-Based Implementation of Precision Medicine. *Frontiers in medicine*, 2022; 9, 757212.

Sifakis EG, Wang K, Zerdes I, Bergh J, Hatschek T, Matikas A, *et al*. 23P Longitudinal evaluation of PAM50 molecular subtypes in patients receiving neoadjuvant HER2-targeted therapy in the PREDIX HER2 trial. *ESMO Open* 2024; 9:103031.

Sireci AN, Patel JL, Joseph L, Hiemenz MC, Rosca OC, Caughron SK, *et al*. Molecular Pathology Economics 101: An Overview of Molecular Diagnostics Coding, Coverage, and Reimbursement: A Report of the Association for Molecular Pathology. *The Journal of molecular diagnostics* 2020; 22(8), 975–993.

Slembrouck L, Darrigues L, Laurent C, Mittempergher L, Delahaye LJ, Vanden Bempt I, *et al*. Decentralization of Next-Generation RNA Sequencing-Based MammaPrint® and BluePrint® Kit at University Hospitals Leuven and Curie Institute Paris. *Transl Oncol* 2019;12:1557–65.

Sota Y, Seno S, Naoi Y, *et al*. IRSN-23 gene diag nosis enhances breast cancer subtype classification and predicts response to neoadjuvant chemotherapy: new validation analyses. *Breast Cancer*. 2025;32(3):566-581.

Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, *et al*. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. *N Engl J Med*. 2018;379(2):111-121.

Tan BKT, Tan LK, Yu K, Tan PH, Lee M, Sii LH, *et al*. Clinical Validation of a Customized Multiple Signature Microarray for Breast Cancer. *Clin Cancer Res* 2008;14:461–9.

Tramm T, Kyndi M, Myhre S, Nord S, Alsner J, Sørensen FB, *et al*. Relationship between the prognostic and predictive value of the intrinsic subtypes and a validated gene profile predictive of loco-regional control and benefit from post-mastectomy radiotherapy in patients with high-risk breast cancer. *Acta Oncol* 2014;53:1337–46.

Van Den Ende NS, Nguyen AH, Jager A, Kok M, Debets R, Van Deurzen CHM. Triple-Negative Breast Cancer and Predictive Markers of Response to Neoadjuvant Chemotherapy: A Systematic Review. *Int J Mol Sci* 2023;24:2969.

Viale G, De Snoo FA, Slaets L, Bogaerts J, Van 'T Veer L, *et al*. Immunohistochemical versus molecular (BluePrint and MammaPrint) subtyping of breast carcinoma. Outcome results from the EORTC 10041/BIG 3-04 MINDACT trial. *Breast Cancer Res Treat* 2018;167:123–31.

Wang L, Li Q, Aushev VN, Neugut AI, Santella RM, Teitelbaum S, *et al*. PAM50- and immunohistochemistry-based subtypes of breast cancer and their relationship with breast cancer mortality in a population-based study. *Breast Cancer*, 2021;28:1235–42.

Watanabe A, Tsunashima R, Kato C, *et al*. Investigation of recurrence prediction ability of EndoPredict® using microarray data from fresh frozen tissues in ER-positive, HER2-negative breast cancer and indication expansion of EndoPredict® from microarray data from fresh-frozen to FFPE tissues. *Breast Cancer*. 2024;31(4):593-606.

Wesseling J, Tinterri C, Sapino A, Zanconati F, Lutke-Holzik M, Nguyen B, *et al*. An international study comparing conventional versus mRNA level testing (TargetPrint) for ER, PR, and HER2 status of breast cancer. *Virchows Arch* 2016;469:297–304.

Whitworth P, Beitsch P, Mislowsky A, Pellicane JV, Nash C, Murray M, *et al*. Chemosensitivity and Endocrine Sensitivity in Clinical Luminal Breast Cancer Patients in the Prospective Neoadjuvant Breast Registry Symphony Trial (NBRST) Predicted by Molecular Subtyping. *Ann Surg Oncol* 2017;24:669–75.

Wuerstlein R, Kates R, Gluz O, Grischke EM, Schem C, *et al*. Strong impact of MammaPrint and BluePrint on treatment decisions in luminal early breast cancer: results of the WSG-PRIMe study. *Breast Cancer Res Treat* 2019;175:389–99.

Zubair M, Wang S, Ali N. Advanced Approaches to Breast Cancer Classification and Diagnosis. *Front Pharmacol* 2021;11:632079.