OPEN ACCESS – ORIGINAL ARTICLE

Concordance Between the Ki-67 and Proliferation Index of Molecular Signature Tests (MammaPrint and OncotypeDX) Among Filipino Patients in two St. Luke's Medical Center Facilities: An Analytical Cross-sectional Study

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ABSTRACT

Background. Breast cancer remains a leading malignancy among women globally. In addition to established factors like histopathology, hormone receptor status, and lymph node involvement, tools such as immunohistochemistry and molecular tests have been developed to assess tumor behavior and recurrence risk.

Objective. This study investigates the concordance between the Ki-67 proliferation index measured by immunohistochemistry and the recurrence risk scores obtained from molecular genomic testing in patients with invasive breast cancer.

Methodology. This cross-sectional study included patients with invasive breast carcinoma at St. Luke's Medical Center from 2019 to 2024, who underwent biopsy or mastectomy, with hormone status and Ki-67 index assessed by immunohistochemistry. All patients also had molecular genomic testing using either MammaPrint or OncotypeDX. Concordance between Ki-67 and the genomic recurrence risk score was evaluated using Kappa statistics, and results were further analyzed according to clinical risk and hormone receptor status.

Results. Fifty-eight (58) patients met the study criteria. Most had grade 2, hormone receptor-positive, HER2-negative, and node-negative tumors, with high clinical risk based on Adjuvant! Online criteria (adapted from the MINDACT trial). The agreement between categorical Ki-67 and molecular recurrence risk was only fair: 66.7% for MammaPrint (kappa = 0.35) and 60% for OncotypeDX (kappa = 0.29) using a 30% Ki-67 cutoff.

Conclusion. There is a fair agreement between Ki-67 and the molecular genomic tests. These findings are consistent with prior studies reporting weak to moderate association. Despite the limited sample size, Ki-67 remains a practical and accessible risk stratification tool, particularly where genomic assays are unavailable. The study supports integrating Ki-67 with clinicopathologic and genomic data to guide therapy, reflecting current best-practice recommendations.

Key words: breast cancer, Ki-67, OncotypeDX, MammaPrint

ISSN 2507-8364 (Online)
Printed in the Philippines.

Received: 19 April 2026.
Accepted: 14 June 2026.
Published online first: 25 June 2026.
https://doi.org/10.21141/PJP.2026.631

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INTRODUCTION

There is an increasing worldwide cancer burden. According to the Global cancer statistics for 2020, an estimated 19.3 million new cancer cases and almost 10 million cancer deaths occurred worldwide. Breast cancer is one of the most prevalent types of cancer and has surpassed lung cancer as the most diagnosed malignancy. Among Filipino women, breast cancer is the most common cause of malignancy accounting for 31.4% of cases. This remains a significant public health concern, particularly in developing countries such as the Philippines.[1-4] When screened, the proportion of breast tumors that are malignant varies depending on the population studied and the diagnostic methods employed. The overall malignancy rates for all breast tumors varies from 10 to 20% but depending on the age and imaging characteristics, studies show that the rates may go as high as 40%.[5-11]

Breast cancer treatment is expensive. Majority of payments for these treatments come from out-of-pocket expenses. Though available, the PhilHealth packages cover only a portion of the total cost of treatment. In a study by Ngelangel et al., approximately PhP 180,000 pesos in out-of-pocket expenditures were spent on cancer treatment. Government agencies help shoulder some of these expenses such as the *Malasakit* center, Breast Cancer Medicine awareness program and the PhilHealth the Z-package, however, the financial burden still exists. Surgery alone entails a big financial burden on the patient. The addition of neoadjuvant or adjuvant chemotherapy causes greater physical, and financial impact to Filipino patients.[1,12,13]

In breast cancer, the clinicopathologic features such as age, tumor size and grade, hormone receptor status, and axillary lymph node involvement affect the treatment protocol for each patient. The National Comprehensive Cancer Network (NCCN) guidelines recommend the determination of biomarkers such as estrogen receptor (ER), progesterone receptor (PR), HER2 status, and testing for Ki-67, especially if hormone receptor-positive, HER2-negative and considering adjuvant abemaciclib.[14] The determination of these biomarkers using immunohistochemistry (IHC) and fluorescence in-situ hybridization (FISH) subclassify breast cancer to its major molecular subtypes: Luminal-types A and B, HER2-enriched, and Triple negative. The luminal subtypes are differentiated according to their hormone receptor expression and Ki-67 expression. Luminal A is ER+, PR high, HER2 -, and Ki-67 <20%, while Luminal B is ER+, PR low or intermediate +, HER2 + or HER2 -, and Ki-67 ≥20%.[15-17] Aside from these, biomarkers such as Ki-67, alongside molecular signature tests like MammaPrint and OncotypeDX, are crucial in guiding the prognosis and treatment planning.

Ki-67 is a nuclear protein associated with cell proliferation. It has been widely used as a prognostic and predictive marker in cancer.[18] Ki67 is expressed in actively dividing cells. Its signal increases as cells move through the different phases of the cell cycle. In tumors, these Ki-67 positive cells generally correlated with more aggressive behavior and worse clinical course.[19,20] It is particularly useful in distinguishing between luminal A and luminal B subtypes, which have different treatment approaches and prognoses.[17,21]

Ki-67 for breast cancer can be used for monitoring neoadjuvant chemotherapy and prognostication purposes. In the 2021 St. Gallen consensus a definite cut-off for recommending chemotherapy in ER-positive node negative breast cancer could not be completely established.[22,23] The recommendations for giving or withholding chemotherapy was only recommended in Ki-67 percentages of <5% or ≥30%. In a study by Huang et al, the most common expression range of Ki-67 in hormone receptor positive, HER2-negative breast cancer is 10-30%.[24] This shows that a great proportion of breast cancer patients will fall into this category, urging us to find a more cost-effective biomarker that can clinch and guide treatment considering all the factors. Several studies have demonstrated that high Ki-67 levels correlate with poorer prognosis and increased likelihood of recurrence.[25,26] However, standardization issues in Ki-67 assessment methods have led to variations in clinical interpretation. Prospective studies that looked onto molecular genomic tests such as MINDACT, ADAPT, TAILORx, and RxPonder were done to fill the gap.[27-30]

MammaPrint and OncotypeDX are genomic assays designed to stratify breast cancer patients based on their risk of recurrence and response to chemotherapy. MammaPrint is a 70-gene expression profile that categorizes patients into high-risk and low-risk groups.[23,24] OncotypeDX, on the other hand, is a 21-gene assay that provides a Recurrence Score (RS) to predict the likelihood of distant recurrence and chemotherapy benefit in hormone receptor-positive, HER2-negative breast cancer patients.[25] Studies have shown that both tests help personalize treatment decisions and reduce unnecessary chemotherapy exposure.[26] One of the largest studies performed is the MINDACT trial (Microarray In Node Negative Disease may Avoid Chemotherapy). This was launched with the aim of prospectively validating the performance of the Amsterdam 70-gene profiler MammaPrint. Using high-throughput microarray analysis, MammaPrint can accurately select early-stage breast cancer patients who are highly likely to develop distant metastases or recurrence and, therefore, may benefit the most from adjuvant chemotherapy. The MammaPrint results were correlated to the clinical risk as well. In the MINDACT trial, low clinical risk in ER+/HER2- breast cancer was defined as a 10-year breast cancer-specific survival probability of greater than 88% without adjuvant systemic therapy. They determined this by using a modified version of Adjuvant! Online, considering tumor size, grade, nodal status, hormone and HER2 receptor status. The low clinical risk was defined by specific criteria for tumor size and grade, with variations depending on the presence or absence of lymph node involvement.[22-24] The use of Mammaprint and other genomic profiling tests such as BluePrint and OncoType DX have been utilized in the Philippines. In a study by Kho et al, all low-risk Filipinos patients in their study underwent adjuvant endocrine therapy alone and foregone otherwise clinically recommended chemotherapy. Gene profiling of breast cancer in a resource-limited setting is feasible and imperative to avoid chemotherapy and/or overtreatment.[27]

It was recognized in the 2021 St. Gallen International Consensus guidelines for treatment of early breast cancer that genomic assays are highly recommended, but they understand that access to such testing is not available to most women around the world. While governance should improve this disparity, the availability of Ki-67 scores may serve as a surrogate for defining proliferation and biological risk.[16] Thus, the concordance of Ki-67 index to the molecular gene panel, MammaPrint and OncotypeDX, can be useful in determining breast cancer treatment. Several studies have explored the relationship between the Ki-67 index and molecular signature tests. A meta-analysis by Petrelli et al. (2015) found a moderate correlation between Ki-67 and OncotypeDX RS, suggesting that while Ki-67 provides valuable proliferation information, molecular assays offer a more comprehensive genomic risk assessment.[28] Additionally, research has shown that Ki-67 alone may not fully capture the tumor's biological complexity, necessitating the integration of molecular tests for a more accurate prognosis.[26] Recent research

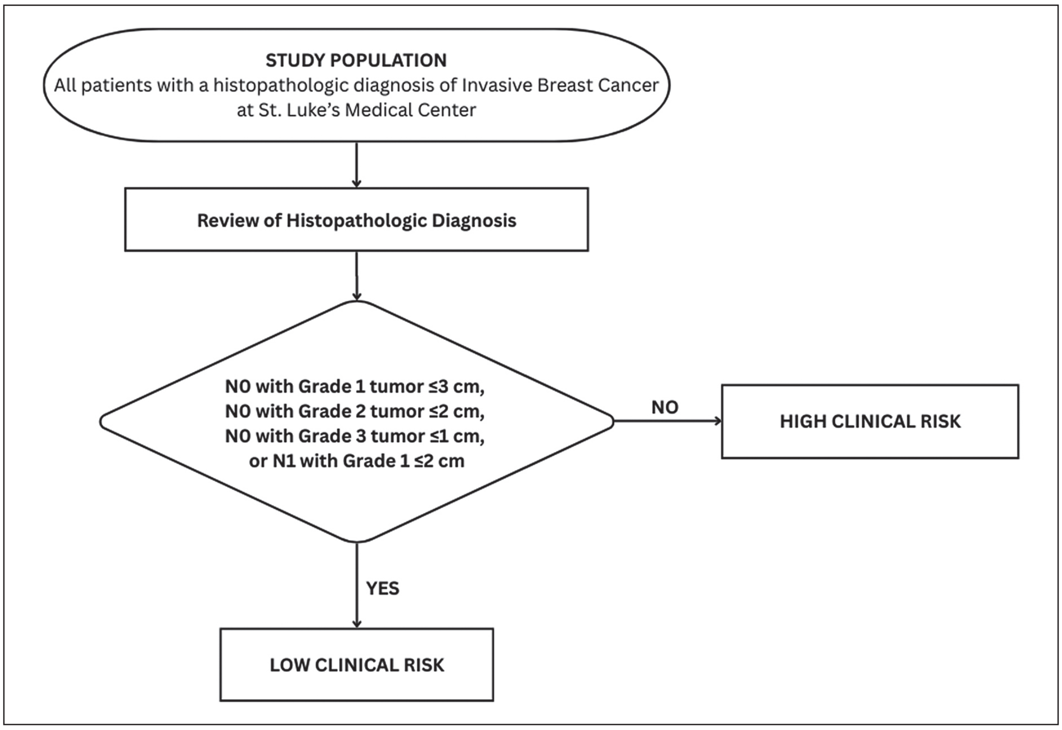

Figure 1. Assignment of clinical risk.

continues to underscore the prognostic value of Ki-67 in breast cancer. A 2023 study by Lee et al., examined the association between Ki-67 levels, the 21-gene Recurrence Score (OncotypeDX), endocrine resistance, and survival outcomes. The study found that higher Ki-67 levels were linked to increased endocrine resistance and poorer survival rates, highlighting Ki-67's role in predicting treatment response and prognosis.[29] The relationship between Ki-67 and molecular assays like OncotypeDX has been further explored in recent studies. Lee et al.,'s 2023 research demonstrated that while both Ki-67 and the 21-gene Recurrence Score are valuable, they provide complementary information. Ki-67 offers immediate proliferation data, whereas molecular assays deliver a broader genomic risk assessment, suggesting that integrating both markers could enhance prognostic accuracy.[28-33]

The Ki-67 proliferation index and molecular signature tests such as MammaPrint and OncotypeDX play vital roles in breast cancer prognosis and treatment stratification. While Ki-67 is a widely accessible marker, molecular tests provide a broader genomic perspective. However, given the high cost and limited accessibility to genomic tests like MammaPrint and Oncotype DX in the Philippines, investigating Ki-67 as a cost-effective surrogate marker to aid clinicians in risk stratification and treatment decisions, especially considering the ethnic and genetic diversity in breast cancer should be explored. Utilizing Ki-67 may also help patients who could benefit from adjuvant chemotherapy, thereby optimizing treatment plans without incurring the high costs associated with genomic testing.[34-37]

The study aimed to evaluate the concordance of Ki-67 index score using immunohistochemistry and the recurrence score using the molecular genomic tests (MammaPrint and OncotypeDX) among Filipino patients with Invasive Breast Cancer seen in SLMC in the said time frame. The concordance between Ki-67 and molecular genomic tests (MammaPrint and OncotypeDX) in determining the risk of recurrence based on Kappa statistics was also analyzed overall, by age group, by clinical risk, by estrogen and progesterone receptor status, and by Her2/neu status. Understanding the concordance between these markers in Filipino patients, may potentially improve individualized breast cancer management in the local setting.

METHODOLOGY

Study design

This is an analytic cross-sectional study which included patients with Invasive Breast Carcinoma in St. Luke's Medical Center (SLMC) from January 1, 2019, to December 31, 2024. Data was collected via retrospective review of medical charts through the hospital's electronic medical records and laboratory information system.

Risk assessment

The clinical risk or the probability of breast cancer survival without systemic therapy was based on the MINDACT trial using the Adjunct Online! tool.[31] Figure 1 illustrates the assigned the risk based on the data from the histopathology report. "Low clinical risk" was defined as: N0 with Grade 1 tumor ≤3 cm, N0 with Grade 2 tumor ≤2 cm, N0 with Grade 3 tumor ≤1 cm, or N1 with Grade 1 ≤2 cm. All other tumor grades or nodal stage that did not fit this category was defined as "high clinical risk."

Inclusion and exclusion criteria

The study included all patients 18 years old and above and must have had their breast biopsy or mastectomy done in SLMC. The histopathology report must have included the diagnosis of Invasive breast carcinoma with reports of the tumor size, histologic grade, histologic subtype, and lymphovascular invasion. Additional pathology reports should also have Ki-67, hormone status (ER, PR), and HER2/neu using IHC or FISH done in the same institution. Only those whose biopsy specimens sent out through the SLMC laboratory for molecular genomic testing for OncotypeDX or MammaPrint were included in the study. Those with incomplete reports and other organs or biopsy sites that were not the breast were excluded from the study.

Sample size

PASS 2021 software was used to compute the minimum sample size requirement. Parameters were obtained from a previous study by Amezcua-Gálvez et al.[38] A minimum of 59 patients were required to achieve 90% statistical power given a kappa of 0.35 and alpha set at 0.05. Although a minimum sample size was computed, the researchers performed total enumeration technique wherein all eligible patients will be included in the study.

Data collection and analysis

Data was encoded in MS Excel by the researcher. Stata MP version 17 software was used for data processing and analysis. Continuous variables were presented as mean/ standard deviation (SD) and median/interquartile range (IQR) depending on the data distribution. Shapiro Wilk test was used to assess the normality of data. Categorical variables were expressed as frequencies and percentages.

The concordance of Ki-67 with MammaPrint and OncotypeDX was examined using percent agreement and Cohen's Kappa statistics. Cohen's kappa was interpreted as poor (<0.00), slight (0.00-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80), and almost perfect (0.81-1.00) agreement. Subgroup analyses by clinical risk was performed. Sensitivity analyses excluding PR- and HER2+ were also done. Missing data were neither replaced nor estimated.

Ethical considerations

This research protocol was reviewed and approved by the St. Luke's Medical Center Institutional Ethics Assess Committee. The study involved retrospective data collection from patients admitted between January 2019 and December 2024, for which a waiver of informed consent was granted due to the absence of direct patient contact. All patient information was anonymized using coded identifiers and securely stored in password-protected electronic files and locked physical cabinets accessible only to authorized personnel. Privacy and confidentiality were maintained throughout, with data remaining for five years before destruction. The research was conducted in accordance with the Declaration of Helsinki (2013) and the ICH-GCP guidelines.

RESULTS

A total of 58 patients were included in the study. Table 1 presents the characteristics of the included patients. The mean age of the cohort was 57.1 years. Based on these criteria, the clinical risk stratification is 43% (n = 25) were considered low risk and 57% (n=33) were categorized as high risk. The median tumor size was 1.6 cm.

Table 1. Demographic and clinical characteristics of invasive breast cancer patients, SLMC

Characteristics	n (%) Mean ± SD
Age (in years), mean	57.1 ± 10.4
<50 years	15 (26)
≥50 years	43 (74)
Clinical risk	
Low risk	25 (43)
High risk	33 (57)
Tumor size (in cm), median	1.6 [IQR: 1.2, 2.5]
Nodal status	
N0	45 (78)
N1	13 (22)
N2	0
N3	0
Histologic grade	
G1	10 (17)
G2	36 (62)
G3	12 (21)
Lymphovascular invasion	
Yes	17 (29)
No	41 (71)
ER	
Positive	58 (100)
Negative	0
PR	
Positive	56 (97)
Negative	2 (3)
HER-2-neu	
Positive	3 (5)
Negative	55 (95)
Ki67, median	30 [IQR: 15, 40]
<30%	28 (48)
≥30%	30 (52)
Mammaprint, mean [n = 33]	-0.1 ± 0.3
Low risk	13 (39)
High risk	20 (61)
Oncotype DX, median [n = 25]	21 [IQR: 14-24]
Low-to-medium risk	20 (80)
High risk	5 (20)

Majority of cases were node-negative (N0) with a histologic grade 2 (G2). Lymphovascular invasion was identified in 29% (n=17) of patients. All tumors were estrogen receptor-positive (ER+, 100%, n=58). Progesterone receptor (PR) status was positive in 97% (n = 56) and negative in 3% (n=2). On HER-2-neu assessment, only 5% (n=3) of tumors were positive, while the majority (95%, n=55) were negative.

The median Ki67 proliferation index in the study was 30%. The percentage of patients who had a Ki-67 greater than 30% was 52% Genomic risk assessment using MammaPrint was performed in 33 patients, yielding a mean score of -0.1 ± 0.3. Thirteen patients (39%) were classified as low-risk and 20 (61%) as high-risk. Oncotype DX testing was carried out in 25 patients, with a median score of 21. Of these, 80% (n=20) fell within the low-to-medium risk category and 20% (n = 5) were identified as high risk.

Table 2. Concordance of Ki67 and MammaPrint (n = 33)

Ki67	Mammaprint		
	High risk	Low risk	Total
≥30%	12	3	15
<30%	8	10	18
Total	20	13	33

Table 3. Concordance of Ki67 and Oncotype DX (n = 25)

Ki67	Oncotype DX		
	High risk	Low-to-medium risk	Total
≥30%	5	10	15
<30%	0	10	10
Total	5	20	25

Concordance of Ki67 and molecular genomic tests

As summarized in Table 2, concordant classification between the Ki-67 proliferation index and MammaPrint genomic risk was observed in 22 of 33 patients, corresponding to an agreement rate of 66.67% (95% CI: 49.69–83.64%). Cohen's kappa was 0.35, indicating fair agreement between the two measures, and this association was statistically significant (p = 0.035).

When comparing Ki-67 and OncotypeDX, concordant results were found in 15 of 25 patients, yielding an agreement rate of 60% (15/25; 95% CI: 39.40–80.64%). All patients with Ki67 <30% (n = 10) were classified as low-to-medium risk by Oncotype DX, while among patients with Ki67 ≥30% (n=15), 5 were high risk and 10 were low-to-medium risk by Oncotype DX. Cohen's kappa statistic for the agreement between Ki67 and Oncotype DX was 0.29, indicating fair agreement, though not statistically significant (p = 0.031).

Concordance of Ki67 and molecular genomic tests by age group

For Ki-67 and MammaPrint, concordance was lower in younger patients, with only 4 of 9 women under 50 years (44.44%; 95% CI, 3.93–84.96%) showing matching risk classifications, corresponding to slight agreement (kappa = 0, p = 1.000). In contrast, among patients aged 50 years and above, 18 of 24 (75.0%; 95% CI, 56.32–93.68%) had concordant results, indicating moderate agreement between Ki-67 and MammaPrint (kappa = 0.50, p = 0.010).

A similar pattern was seen for Ki-67 and Oncotype DX: in those younger than 50 years, 4 of 6 patients (66.67%; 95% CI, 12.47–100%) showed concordance, reflecting fair agreement (kappa = 0.33, p = 0.337). Among patients ≥50 years, concordant Ki-67 and Oncotype DX classifications were observed in 11 of 19 cases (57.89%; 95% CI, 33.45–82.34%), also consistent with fair agreement (kappa = 0.27, p = 0.067).

Concordance of Ki67 and molecular genomic tests by clinical risk

In subgroup analyses by clinical risk, Ki-67 showed different patterns of concordance with the two genomic assays. For Ki-67 and MammaPrint, agreement was higher in the low-risk group: 10 of 13 low clinical risk patients (76.92%; 95% CI, 50.42–100%) had concordant results, with moderate agreement (kappa = 0.53, p = 0.051), compared with 12 of 20 high-risk patients (60.00%; 95% CI, 36.48–83.52%) and only fair agreement (kappa = 0.24, p = 0.198). In contrast, for Ki-67 and Oncotype DX, the concordance tended to be better in the high-risk group, where 9 of 13 patients (69.23%; 95% CI, 40.20–98.26%) showed concordant classifications with moderate agreement (kappa = 0.43, p = 0.052). Among low clinical risk patients, only 6 of 12 (50.00%; 95% CI, 16.82–83.18%) had concordant Ki-67 and Oncotype DX results, corresponding to slight agreement (kappa = 0.12, p = 0.356).

Concordance of Ki67 and molecular genomic tests by receptor status

Sensitivity analyses were conducted in hormone receptor–positive, HER2-negative subgroups, as all tumors were ER-positive, and the small number of HER2-positive cases (n = 3) precluded meaningful separate analysis. Among PR-positive patients assessed with Ki-67 and MammaPrint (n = 33), 22 showed concordant risk classifications, corresponding to an agreement of 66.67% (95% CI, 49.69–83.64%) and fair agreement (kappa = 0.35, p = 0.035). Similarly, for PR-positive patients evaluated with Ki-67 and

Table 4. Concordance of Ki67 and MammaPrint by age group

Ki67	<50 years (n = 9)			≥50 years (n = 24)		
	Mammaprint			Mammaprint		
	High risk	Low risk	Total	High risk	Low risk	Total
≥30%	2	1	3	10	2	12
<30%	4	2	6	4	8	12
Total	6	3	9	14	10	24

Table 5. Concordance of Ki67 and Oncotype DX by age group

Ki67	<50 years (n = 9)			≥50 years (n = 24)		
	Oncotype DX			Oncotype DX		
	High risk	Low-to-medium risk	Total	High risk	Low-to-medium risk	Total
≥30%	1	2	3	4	8	12
<30%	0	3	3	0	7	7
Total	1	5	6	4	15	19

Table 6. Concordance of Ki67 and MammaPrint by clinical risk

Ki67	High clinical risk (n = 20)			Low clinical risk (n = 13)		
	Mammaprint			Mammaprint		
	High risk	Low risk	Total	High risk	Low risk	Total
≥30%	8	1	9	4	2	6
<30%	7	4	11	1	6	7
Total	15	5	20	5	8	13

Table 7. Concordance of Ki67 and Oncotype DX by clinical risk

Ki67	High clinical risk (n = 13)			Low clinical risk (n = 12)		
	Oncotype DX			Oncotype DX		
	High risk	Low-to-medium risk	Total	High risk	Low-to-medium risk	Total
≥30%	4	4	8	1	6	7
<30%	0	5	5	0	5	5
Total	4	9	13	1	11	12

Oncotype DX (n = 23), 14 had concordant results, yielding an agreement of 60.87% (95% CI, 39.29–82.45%) and again a fair level of agreement (kappa = 0.30, p = 0.033).

A comparable pattern was observed when the analyses were restricted to HER2-negative patients. Among the 30 HER2-negative women who underwent both Ki-67 and MammaPrint testing, 20 had concordant classifications (66.67%; 95% CI, 48.76–84.57%), with fair agreement (kappa = 0.35, p = 0.048). In the HER2-negative subgroup assessed with Ki-67 and Oncotype DX (n = 25), concordance was seen in 15 patients, corresponding to an agreement of 60.00% (95% CI, 39.36–80.64%) and fair agreement (kappa = 0.29, p = 0.031). Overall, concordance between Ki-67 and both genomic assays remained consistently in the fair range across PR-positive and HER2-negative subgroups, with slightly higher agreement rates for MammaPrint than for Oncotype DX.

DISCUSSION

This study appraises the real-world concordance between the Ki-67 proliferation index determined by immunohistochemistry and risk strata from molecular signature assays—specifically MammaPrint and OncotypeDX—in Filipino patients with predominantly hormone receptor-positive, node-negative, early-stage breast cancer.

Clinical and genomic risk stratification in a Filipino context

Consistent with global epidemiologic trends reported in GLOBOCAN and CA: A Cancer Journal for Clinicians, breast cancer remains the most frequently diagnosed malignancy among women in the Philippines and a major contributor to cancer mortality, underscoring the need for context-appropriate risk stratification strategies.[2-4,39,40] In our cohort, most cases were hormone receptor-positive, node-negative, early-stage tumors, mirroring the profile of contemporary HR-positive/HER2-negative populations in large international trials and registry studies, but genomic testing revealed a spectrum of recurrence risk despite this apparently favorable clinicopathologic profile.

Our findings further demonstrate that most of Filipino patients treated in this tertiary center are categorized as high clinical risk and would traditionally be considered candidates for adjuvant chemotherapy. Clinical risk in this study was assigned using the modified Adjuvant! Online–

Table 8. Concordance of Ki67 and MammaPrint among PR+ patients (n = 33)

Ki67	Mammaprint		
	High risk	Low risk	Total
≥30%	12	3	15
<30%	8	10	18
Total	20	13	33

Table 9. Concordance of Ki67 and Oncotype DX among PR+ patients (n = 23)

Ki67	Oncotype DX		
	High risk	Low-to-medium risk	Total
≥30%	5	9	14
<30%	0	9	9
Total	5	18	23

Table 10. Concordance of Ki67 and MammaPrint among HER2- patients (n = 30)

Ki67	Mammaprint		
	High risk	Low risk	Total
≥30%	10	3	13
<30%	7	10	17
Total	17	13	30

Table 11. Concordance of Ki67 and Oncotype DX among HER2- patients (n = 25)

Ki67	Oncotype DX		
	High risk	Low-to-medium risk	Total
≥30%	5	10	15
<30%	0	10	10
Total	5	20	25

based approach adopted in the MINDACT trial, which integrates age, tumor size, nodal status, histologic grade, and hormone receptor status to estimate relapse risk and to compare clinicopathologic risk with genomic signatures such as MammaPrint. This approach is comparable to other breast cancer clinical decision support systems (CDSSs)—including PREDICT, ONCOassist, CancerMath, CTS5, and residual cancer burden calculators—which similarly combine standard prognostic variables to refine adjuvant treatment recommendations. A systematic review by Mazo et al., reported that CDSSs improve consistency and transparency in complex adjuvant therapy decisions, particularly when used alongside multigene assays such as Oncotype DX and MammaPrint, although further integration of individualized and real-world data is needed to optimize their impact on patient outcomes.[41]

The molecular genomic assays utilized in this study includes MammaPrint and OncotypeDX. Data from prior studies indicate that both assays facilitate individualized treatment decision-making and help reduce unnecessary chemotherapy administration. MammaPrint employs a 70-gene signature to stratify patients into high-risk and low-risk categories, whereas OncotypeDX analyzes a 21-gene panel to generate a Recurrence Score (RS) for prognostication and therapeutic guidance.[29-31] Although standardized treatment algorithms, such as those outlined in the NCCN Clinical Practice Guidelines, provide a framework for managing early breast cancer, molecular assays refines a more precise clinical risk estimates beyond traditional factors like tumor size, grade, nodal status, and hormone receptor profile.[14,15]

Biomarker concordance and clinical interpretation

Based on the 2021 St. Gallen International Consensus, adjuvant chemotherapy in ER-positive, HER2-negative, node-negative breast cancer is most clearly supported at the extremes of proliferation, with Ki-67 values ≤5% arguing against chemotherapy and Ki-67 ≥30% favoring its use.[16] Because no institutional cutoff had been established, we adopted the ≥30% threshold recommended by St. Gallen to define a high Ki-67 category in our cohort. Using this cutoff, we observed only fair concordance between Ki-67 and the molecular genomic assays, with agreement rates of 66.7% for MammaPrint (kappa = 0.35) and 60.0% for Oncotype DX (kappa = 0.29).

This modest agreement aligns with prior reports showing weak to moderate correlation between Ki-67 and multigene signatures, including studies and meta-analyses indicating that Ki-67 alone cannot fully recapitulate the composite genomic risk captured by assays such as Oncotype DX and MammaPrint. Several series have reported low or non-significant linear correlations between Ki-67 and the 21-gene Recurrence Score, despite both being proliferation-linked, and kappa coefficients in the low to fair range when dichotomized risk groups are compared. Taken together with our data, these findings support the use of Ki-67 as a helpful, accessible surrogate marker, but reinforce that treatment decisions should ideally integrate Ki-67 with clinicopathologic features and, where available, genomic assay results rather than relying on Ki-67 alone.[22,23,29,30,42-45]

Technical limitations in Ki-67 assessment likely contribute substantially to the discordance we observed between Ki-67 and multigene assays. Antibody clone selection, fixation and staining protocols, pre-analytical handling, subjective visual scoring, and the lack of universally adopted thresholds (and alignment between manual and digital image analysis) are all well-described sources of variability.[46] Studies by Copur et al. and Selmani et al., have reported only low to moderate concordance between Ki-67 and Oncotype DX, regardless of whether Ki-67 is measured by conventional immunohistochemistry or more quantitative approaches, underscoring that technical and methodological differences limit interchangeability.[30,42] Further comparisons, including those by Tian et al., Nguyen et al, and Pons et al., reinforce that heterogeneity in Ki-67 scoring methods and population differences impact reliability and interchangeability across molecular and protein markers.[44-46] To mitigate these issues in our study, we restricted inclusion to these two tertiary centers with uniform tissue processing and IHC protocols, with most Ki-67 readings were rendered by one pathologist, which likely reduced—but did not eliminate—measurement variability.

Subgroup analyses suggested that patient characteristics also modulate concordance patterns. Among women aged ≥50 years, Ki-67 and MammaPrint showed moderate agreement, whereas only slight agreement was seen in those <50 years, a difference that is probably influenced by the very small number of younger patients and wide confidence intervals in this group. This age-related trend is compatible with prior reports that proliferation indices and genomic risk scores may behave differently in younger versus older hormone receptor-positive cohorts, particularly where chemotherapy benefit and endocrine sensitivity differ.[41,42]

When stratified by clinical risk, agreement between Ki-67 and MammaPrint was highest in the low clinical risk group (moderate agreement, kappa = 0.53) and only fair in the high-risk group (kappa = 0.24), suggesting that Ki-67 may align better with genomic risk at the more favorable end of the spectrum. In contrast, Ki-67 and Oncotype DX showed the opposite pattern, with moderate agreement in clinically high-risk patients and only slight agreement in those at low clinical risk (kappa = 0.12, p = 0.356), indicating that the two genomic platforms may weigh proliferative and non-proliferative genes differently across risk strata. Similar 'fair' levels of concordance were observed in sensitivity analyses restricted to PR-positive and HER2-negative subgroups, reinforcing the notion that Ki-67 and multigene assays capture overlapping but distinct dimensions of tumor biology rather than being directly interchangeable measures.

Our findings are consistent with meta-analyses and key primary studies that attribute discrepancies between Ki-67 and multigene assays to technical variability, differences in laboratory protocols, inter-observer subjectivity, heterogeneous laboratory practices, and the absence of universally applied cut-offs. Recognizing these challenges, the International Ki-67 in Breast Cancer Working Group and related expert panels have issued detailed recommendations to standardize pre-analytical handling, scoring methodology, and reporting of Ki-67, with the goal of improving reproducibility, enabling more reliable cross-study comparisons, and clarifying how Ki-67 should be integrated with genomic assays in routine practice.[22,23,29,30,42-48]

Limitations and directions for future research

The relatively small sample size limited the power of this study to perform more granular subgroup analyses, and the retrospective design may have introduced selection bias. In addition, only a subset of eligible patients underwent molecular genomic testing, reflecting both physician-driven test ordering and substantial out-of-pocket costs, which in the Philippines are estimated at approximately PHP 200,000–300,000 (USD 3,000–5,000) per assay. Even in a tertiary center such as St. Luke's Medical Center, multigene assays are not requested routinely, further constraining the number of cases available for concordance analyses. Another limitation is that we were unable to correlate Ki-67 and genomic test results with long-term outcomes such as recurrence or metastasis, preventing direct comparison of their prognostic performance in this cohort. Prospective studies with larger, more diverse populations and systematic follow-up will be necessary to clarify how surrogate markers like Ki-67 relate to in-vivo tumor biology and to validate their use alongside, or in place of, multigene assays in resource-constrained settings.

CONCLUSION

Given persistent financial barriers in the Philippines, Ki-67 remains a pragmatic and widely accessible option for initial risk stratification in settings where multigene assays cannot be routinely performed. However, our findings support integrating Ki-67 with clinicopathologic and genomic information whenever feasible, in line with contemporary best-practice recommendations.[14-16,28,31] Consistent with the ESMO guidelines for early breast cancer, pretreatment assessment should include histological type and grade, IHC evaluation of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) biomarkers and a proliferation marker such as Ki-67. Furthermore, gene expression assays (e.g., EndoPredict, MammaPrint, Oncotype DX, Prosigna and others) are primarily recommended for HR-positive, HER2-negative tumors at immediate clinical risk based on conventional pathology and IHC, and only one of these assays should be used for each individual patient.[48]

Looking forward, research must focus on optimizing Ki-67 cut-offs for Filipino and broader Southeast Asian populations, ensuring assay standardization, and further validating risk models that accommodate local clinical realities and resource limitations. And while Ki-67 and further molecular genomic tests have yet to be included in the National Clinical Practice Guidelines for Breast Cancer, collaboration between clinicians, pathologists, and health policymakers—especially those involved in national health insurance reforms and cancer access programs—will be key to implementing findings from cutting-edge genomic research for the benefit of Filipino patients.[49]

ACKNOWLEDGMENTS

The authors thank the Institute of Pathology and Institutional Ethics Review Committee of the St. Luke's Medical Center for their technical support, assistance, and unwavering support of research.

STATEMENT OF AUTHORSHIP

The authors certified fulfillment of ICMJE authorship criteria.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are retained at St. Luke's Medical Center. Restrictions apply to the availability of these data, which were used under license/ethical approval for the current study, and so are not publicly available. Data requests may be submitted to the Institutional Ethics Review Committee of St. Luke's Medical Center for researchers who meet the criteria for access to confidential data.

AUTHOR DISCLOSURE

The authors declared no conflicts of interest.

FUNDING SOURCE

None.

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