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ORIGINAL ARTICLE

The clinical impacts of molecular subtyping by multigene assay on hormone receptor-positive breast cancers

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Abstract

Background: Multigene assays, such as MammaPrint and BluePrint, provide additional information other than conventional immunohistochemistry (IHC) to help making decision of treatment. This study aims to compare the clinical correlation between molecular subtyping (MS) versus surrogate pathological subtyping (PS).

Methods: A database from patients receiving MS evaluation in Taipei Veterans General Hospital from 2013 to 2018 was reviewed retrospectively. Patients were categorized as luminal A, luminal B, human epidermal growth factor receptor 2 (HER2) and basal type from MS results and also centrally assessed according to PS (estrogen receptor [ER], progesterone receptor [PgR], HER2, and Ki-67). The clinical correlation between two different subtyping methodologies was analyzed, and the application of chemotherapy was compared.

Results: From 2013 to 2018, a total of 130 patients received MS testing in our institute, and 132 tumor samples were sent for analysis. From MammaPrint, 64 (48.5%) and 55 (41.7%) samples were defined as low and high risks, respectively. The other 13 (9.8%) tumor samples were identified as late recurrence low risk. MS restratified 44 tumors as subtype shifting including 20 tumors from A to B in intrinsic subtypes and 24 tumors from B to A after MS evaluation. Chemotherapy was conducted in only one (1.3%) patient with MS-luminal A but in 87.8% (n = 43) of MS-luminal B subtypes.

Conclusion: The MS results restratify the subtypes of hormone receptor positive breast cancer and dominate decision-making of adjuvant therapy. The role of surrogate biomarkers as an alternative tool needs further elucidation. The treatment outcome in different subtypes categorized by MS or PS will be the interesting focus of research.

Keywords: Breast neoplasm; Immunohistochemistry; Receptors, progesterone; Receptors, estrogen

1. INTRODUCTION

Nowadays, treatment for breast cancer is towards tailored therapy according to subtype categorization. Breast cancer subtyping helps physicians to predict the prognosis of each patient and vary the strategy of treatment. The current edition of AJCC (8th) enhances the concept of subtype grouping in definition of staging.[1] However, it remains controversial that which methodology can precisely classify subtype grouping. Traditionally, we apply immunohistochemistry (IHC) to provide information of estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2), and Ki-67 as the widely used biomarkers to help treatment allocation in clinical practice. Nowadays, molecular subtyping (MS) attracts more attention based on its value in precision medicine.

Within the currently available multigene expression assays, MammaPrint is based on a 70-gene prognostic signature that determines the messenger ribonucleic acid (mRNA) levels of genes to discriminate the risk of recurrence,[2,3] whereas BluePrint is also an RNA-based and 80-gene assay designed to classify breast cancer patients into Basal-type, Luminal-type, and HER2-type subgroups.[4] Seventy-gene MammaPrint is applied in coordination with clinical risks to determine the role of adjuvant chemotherapy, and BluePrint 80-gene profile helps in bridging MS and treatment response. The two profiles that use the same platform provide informative signatures to identify the intrinsic molecular subtypes based on a tumor's functional pathway and risk assessment.[5] MammaPrint was first validated by four independent cohorts with 784 patients[4] and well accepted after its landmark randomized, prospective, phase III clinical trial known as MINDACT study, which demonstrated the possibility

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of omission from chemotherapy in a proportion of breast cancer patients who are at high clinical risk.[6]

Although chemotherapy maintains its power in reducing the recurrence risk of advanced stage, controversy still exists in patients with intermediate risk factors such as strong positivity for hormone receptors or low tumor burden.[7] The selection of low-risk patients to omit chemotherapy turns into a challenging issue especially in hormone-positive breast cancer. Whether endocrine responsiveness can be only judged by positivity of hormone receptor, grade or Ki-67 is also questioned, especially when the potential of interlaboratory variation may exist in interpretation of Ki-67. Therefore, multigene assays gradually become the choice for decision-making, especially in those with borderline risks in clinical or histopathological features. However, not every patient could afford the high expense of multigene assays in real world. Most patients can only rely on the surrogate biomarkers, including ER, PR, HER2, and Ki-67, which are also named as IHC4, to categorize the pathological subtypes (PS). Here, we aim to compare the clinical correlation between MS and PS and review the impacts of multigene assays in clinical practice.

2. METHODS

2.1. Study Population

All patients with early breast cancer receiving operation in our institution and referred to MS evaluation between 2013 and 2018 were recruited into study. All analytic data were retrieved from our breast cancer database, which was established in 2000. The flow chart of patient selection is shown in Supplementary Figure 1, http://links.lww.com/JCMA/A127. In the same period between 2013 and 2018, a total of 2023 patients with stage I or II disease and positive hormone receptor who indicated for multigene assays were inspected for this research. Since the multigene assay was not reimbursed by national health insurance in Taiwan, only 130 (6.4%) patients were able to afford the expense of testing. Patients who had borderline risks in recurrence were introduced to multigene assays and took the testing based on their own request. Meanwhile, 1893 patients who have not received multigene assay were recommended to have treatment following shared decision-making and guidelines of our institute. The MS results, clinical information including choices of surgery, chemotherapy, and hormone therapy, and pathological features, such as histological grade, ER, PR, HER2, and Ki-67, were analyzed. The study was approved by the institutional review board of Taipei Veterans General Hospital. All the data were collected without direct contact with patients, as such written consent from study subjects was waived by the institutional review board.

2.2. Allocations of Breast Cancer Subtypes

All the tumor samples were processed and interpreted by one pathologist (C.-Y. Hsu) following the ASCO/CAP guideline recommendation. The original IHC stains for ER (clone 6F11, 1:100; Leica Biosystems, Newcastle, United Kingdom), PR (clone 16, 1:150; Leica Biosystems), HER2 (A0485; Dako, Glostrup, Denmark, 1:900), and Ki-67 (clone MIB-1, 1:75; Dako) were evaluated without knowledge of 70-gene assay results. Positive ER and PR staining were defined as ≥1% tumor cells that exhibit nuclear staining.[8] HER2 positivity was regarded when either IHC 3+ or gene amplification was shown by FISH according to CAP/ASCO recommendation.[9] The percentage of Ki-67–positive tumor cells was calculated from at least three high-power fields (×400) and averaged for the Ki-67 labeling index using manual counting or image analysis (ImmunoRatio).[10,11] Patients were allocated into different PS according to the 2011 St. Gallen International Breast Cancer Expert Panel guidelines: luminal A (ER- and/or PR-positive, HER2-negative, Ki-67 low, and histological grade 1 or 2); luminal B (ER- and/or PR-positive, Ki-67 high, or grade 3 or HER2-positive), HER2 type (ER- and/or PR-negative and HER2-positive), triple-negative (ER-negative, PR-negative, and HER2-negative).[12] However, all MS evaluation was centrally assessed on the excisional specimen and also categorized into intrinsic types, as mentioned above. The clinical correlation between two different subtyping methodologies was analyzed, and the treatment choices, such as hormone therapy or chemotherapy, was compared.

2.3. IHC-Based Prognosis Models

In order to extend the clinical utilization of surrogate biomarkers, we applied three models to calculate IHC4 scores based on previous study investigated by one of our authors (C.-Y. Hsu).[13] The results of three models allocated patients into low, intermediate, and high risk, and the correlation among three IHC-based prognosis models and MS was analyzed.

2.4. Statistical Analysis

Descriptive statistical analysis was applied to compare the baseline characteristics among the risk assessment and clinicopathologic features. Categorical data were summarized in counts and percentages. χ^2 test was used to compare the distributions of categorical variables, and Pearson correlation was used to study the correlation coefficient between two variables. A two-sided p value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (version 19.0, SPSS, Chicago, IL).

3. RESULTS

3.1. Characteristics of Low- vs High-Risk Group in MS

Combined MammaPrint and BluePrint readout was available from 130 patients with 132 tumor samples. The clinical demographics are summarized in Table 1. Nearly all patients, except one, had ER-positive breast cancer, and most of them (82.3%, n = 107) presented strong positivity of ER higher than 90%. Among these, 39 (29.5%) samples were accompanied with metastases in axillary lymph nodes but none of them was involved of >4 lymph nodes. From risk assessment by MammaPrint, 77 (58.3%) tumors were categorized as low risk (n = 64) or late recurrence low risk (n = 13), and 55 (41.7%) were in high risk. Notably, two patients had sent a dual sample concomitantly for analysis, and both of them had discordance in risk assessment from their sampling tissues. One patient had multi-centric tumors in ipsilateral breast, and the other one had bilateral breast malignancy, which presented low risk in the left breast tumor but high risk in the right side.

3.2. Characteristics of Intrinsic Subtypes

According to BluePrint and MammaPrint (Molecular) subtyping, 57.5% of the tumors were luminal A, 37.1% were luminal B, 3% were HER2-enriched, and 2.4% were basal type (Table 2). In univariate analysis, only the presence of lymphovascular invasion and tumor necrosis had significant differences in distribution between subtypes. There was less presence of lymphovascular invasion or tumor necrosis in most intrinsic luminal A subtype tumors. No significant difference was found in other factors, such as histologic types, grade, lymph node involvement, or stage.

3.3. Concordance Between MS and PS

PS stratified 73 (55.3%) tumors as luminal A and 58 (43.9%) tumors as luminal B, and the comparison between MS and PS was listed in Table 3. After MS evaluation, there were 50 (37.9%) tumors had different allocation in intrinsic subtypes,

Table 1

Clinical demographics of 132 samples, low vs high risk in MammaPrint

Characteristics, n (%)	MammaPrint risk		*p*
	Low risk + late recurrence low risk (n = 77)	High risk (n = 55)	
Median age, y (range)	54.5 (35-83)	48 (27-76)	
Tumor type			
IDC	70 (90.9%)	52 (94.5%)	0.465
ILC	5 (6.5%)	3 (5.5%)	
Other	2 (2.6%)	0	
Tumor size			
<2 cm	45 (58.4%)	39 (70.9%)	0.134
2-5 cm	32 (41.6%)	15 (27.3%)	
>5 cm	0	1 (1.8%)	
Stage			
I	34 (44.2%)	31 (56.4%)	0.310
IIA	32 (41.6%)	16 (29.1%)	
IIB	11 (14.3%)	8 (14.5%)	
Lymph nodes			
0	54 (70.1%)	38 (69.1%)	0.494
1-3	23 (29.9%)	16 (29.1%)	
Missing	…	1 (1.8%)	
Grade			
I	12 (15.6%)	4 (7.3%)	0.007
II	64 (83.1%)	42 (76.4%)	
III	1 (1.3%)	9 (16.4%)	
LVI			
Absent	61 (79.2%)	44 (80.0%)	0.623
Present	15 (19.5%)	9 (16.4%)	
Missing	1 (1.3%)	2 (3.6%)	
Tumor necrosis			
Absent	57 (74.0%)	27 (49.1%)	0.003
Present	18 (23.4%)	28 (50.9%)	
Missing	2 (2.6%)	…	
TIL			
<10	44 (57.1%)	21 (38.2%)	0.090
10-60	23 (29.9%)	22 (40.0%)	
>60	0	0	
Missing	10 (13.0%)	12 (21.8%)	
Hormone receptor			
Positive	77 (100%)	54 (98.2%)	0.235
Negative	0	1 (1.8%)	
HER2			
Positive	0	1 (1.8%)	0.235
Negative	77 (100%)	54 (98.2%)	
Surgery			
BCS	50 (64.9%)	32 (58.2%)	0.430
MRM	27 (35.1%)	23 (41.8%)	
Treatment			
With CT	1 (1.3%)	47 (85.5%)	<0.001
Without CT	76 (98.7%)	7 (12.7%)	
ET	77 (100%)	54 (98.2%)	0.235

IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; LVI = lymphovascular invasion; TIL = tumor infiltrating lymphocyte; HER2 = human epidermal growth receptor 2; BCS = breast conserving surgery; MRM = modified radical mastectomy; CT = chemotherapy; ET = endocrine therapy

including 4 tumors categorized as HER2 type and 2 tumors as TNBC. Notably, MS restratified 44 tumors among luminal subtypes. A total of 20 (27.4%) tumors had subtype shifting from A to B in intrinsic subtypes, and 24 (41.4%) luminal B tumors per PS were restratified as luminal A after MS evaluation (Fig. 1).

3.4. Correlation Between IHC-Based Prognostic Models vs MS

All three models of IHC-based equations had significant difference in stratification compared with MS (Table 4). In IHC4 classification, 81.6% of low-risk group belonged to luminal A in MS, and 80% of high-risk group was regarded as luminal B in MS. The similar distribution was also found in the models of IHC4-Ki67x4 or IHC4 Veterans General Hospital (VGH) cutoff. Notably, most patients were defined as intermediate risk except that in the model of IHC4-Ki67x4. In addition, the correlation among the three models and MammaPrint only showed moderate correlation (R = –0.382 to –0.361).

Table 2

Clinicopathological factors in different molecular subtypes

	Molecular subtyping (BluePrint + MammaPrint)				
	Luminal A	Luminal B	HER2	Basal	
	BluePrint "Luminal" + MammaPrint	BluePrint "Luminal" + MammaPrint	BluePrint "HER2"	BluePrint "Basal"	
Characteristic, n (%)	Low risk (n = 76)	High risk (n = 49)	(n = 4)	(n = 3)	*p*
Age (range), y	55.4	52	55.6	63.1	
Tumor type					
IDC	69 (90.8%)	47 (95.9%)	3 (75.0%)	3 (100.0%)	0.595
ILC	5 (6.6%)	2 (4.1%)	1 (25.0%)	0	
Other	2 (2.6%)	0	0	0	
Tumor size					
<2 cm	44 (57.9%)	33 (67.3%)	4 (100.0%)	3 (100.0%)	0.287
2-5 cm	32 (42.1%)	15 (30.6%)	0	0	
>5 cm	0	1 (2%)	0	0	
Lymph nodes					
0	53 (69.7%)	32 (65.3%)	4 (100.0%)	3 (100.0%)	0.545
1-3	23 (30.3%)	16 (32.7%)	0	0	
Missing	…	1 (2.0%)	…	…	
Stage					
I	33 (43.4%)	25 (51.0%)	4 (100.0%)	3 (100.0%)	0.187
IIA	32 (42.1%)	16 (32.7%)	0	0	
IIB	11 (14.5%)	8 (16.3%)	0	0	
Grade					
I	12 (15.8%)	4 (8.2%)	0	0	0.083
II	63 (82.9%)	37 (75.5%)	4 (100.0%)	2 (66.7%)	
III	1 (1.3%)	8 (16.3%)	0	0	
LVI					
Absent	60 (78.9%)	39 (79.6%)	4 (100.0%)	2 (66.7%)	0.022
Present	15 (19.7%)	9 (18.4%)	0	0	
Missing	1 (1.3%)	1 (2.0%)	…	1 (33.3%)	
Tumor necrosis					
Absent	57 (75.0%)	25 (51.0%)	1 (25.0%)	1 (25.0%)	0.024
Present	17 (22.4%)	24 (49.0%)	3 (75.0%)	3 (75.0%)	
Missing	2 (2.6%)	…	…	…	
TIL					
<10	44 (57.9%)	21 (42.9%)	0	0	0.001
10-60	22 (28.9%)	20 (40.8%)	3 (75.0%)	0	
>60	0	0	0	0	
Missing	10 (13.2%)	8 (16.3%)	1 (25.0%)	3 (100.0%)	

Basal = basal-like; HER2 = human epidermal growth receptor 2; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; LVI = lymphovascular invasion; TIL = tumor infiltrating lymphocyte.

3.5. Impacts on Adjuvant Treatment

The treatment choices for patients with different subtypes are depicted in Fig. 2 according to MS and PS. The proportion of the MS population who underwent adjuvant chemotherapy were 1.3% in luminal A and 87.8% in luminal B. In contrast, although 18 (24.7%) luminal A tumors in PS received chemotherapy, all of them were categorized as luminal B from MS. Only one in four patients with HER2 subtype tumor received chemotherapy, but all three patients with intrinsic basal-type tumor also underwent chemotherapy. In 39 samples harboring metastasis in lymph nodes, 12 were luminal B in PS and 5 of them shifted subtype to luminal A tumors after MS evaluation. All of the five patients did not receive chemotherapy even clinical high risk based on lymph node metastasis.

4. DISCUSSION

Here, we demonstrated that multigene assays restratify 41.4% of our patients with a luminal B subtype in PS into low-risk luminal A subtype. This finding is close to previous evidence reported by the well-known MINDACT trial, which found that MS restratify 54% of patients.[14] In terms of low risk, the indication of chemotherapy may be omitted because of the insignificant benefit in decreasing recurrence or distant metastasis. In our study, the 24 patients restratified into luminal A subtype after MS, none received chemotherapy for adjuvant treatment, but they all had comparable outcomes without disease recurrence (data not shown). The restratification affects clinical decision and results in significantly less patients with a luminal A subtype receiving chemotherapy. Moreover, 5 patients in luminal B in PS with lymph node involvement had subtype shifting and omitted chemotherapy. In contrast, 20 (27.4%) with luminal A subtype in PS were restratified as luminal B after MS, and chemotherapy was conducted in most patients, except for three due to small tumor size of <1 cm or because of personal reason. Before multigene assays, those patients with high clinical risks, such as large tumor size or positive lymph node, are often treated with chemotherapy to avoid recurrence, and some intrinsic aggressive subtypes may be misread as low-risk group. Here, we demonstrated that how multigene assays alter the allocation of subtypes and the decision-making of treatment.

The clinical impacts on decision-making of adjuvant therapy mostly focused on 21-gene signature (Oncotype DX) in

Table 3

Concordance between molecular and pathological subtyping

Pathological subtyping	Molecular subtyping (BluePrint + MammaPrint)				Total
	Luminal A	Luminal B	HER2	Basal	
Luminal A	52 (71.2%)	20 (27.4%)	1 (1.4%)	0	73
Luminal B	24 (41.4%)	29 (50.0%)	3 (5.2%)	2 (3.4%)	58
Triple negative	0	0	0	1 (100%)	1
Total	76	49	4	3	132

Basal = basal-like; HER2 = human epidermal growth factor receptor 2.

the current published literature. Previous report of the WSG-PRIMe Study revealed that recommendation for chemotherapy was switched in 29.1% of cases after MammaPrint/BluePrint testing.[15] In addition, in a total of 452 enrolled cases, 34% of patients were discordant in luminal subtype between BluePrint and IHC assessment. In another study, the IMPACt trial found that the treatment decision was changed in 24% (86/358) of patients after testing.[16] In our study, although the pre-test assessment for chemotherapy recommendation was lacking, significantly less chemotherapy was conducted in luminal A subtype after MS restratification, which made physicians and patients more confident in omission of chemotherapy. Following the coming era of precision medicine, tailored therapy is favored to precisely concur the tumor and avoid side effects from unnecessary treatment. As the mounting evidence from retrospective validation to clinical trials, we now have more confidence to

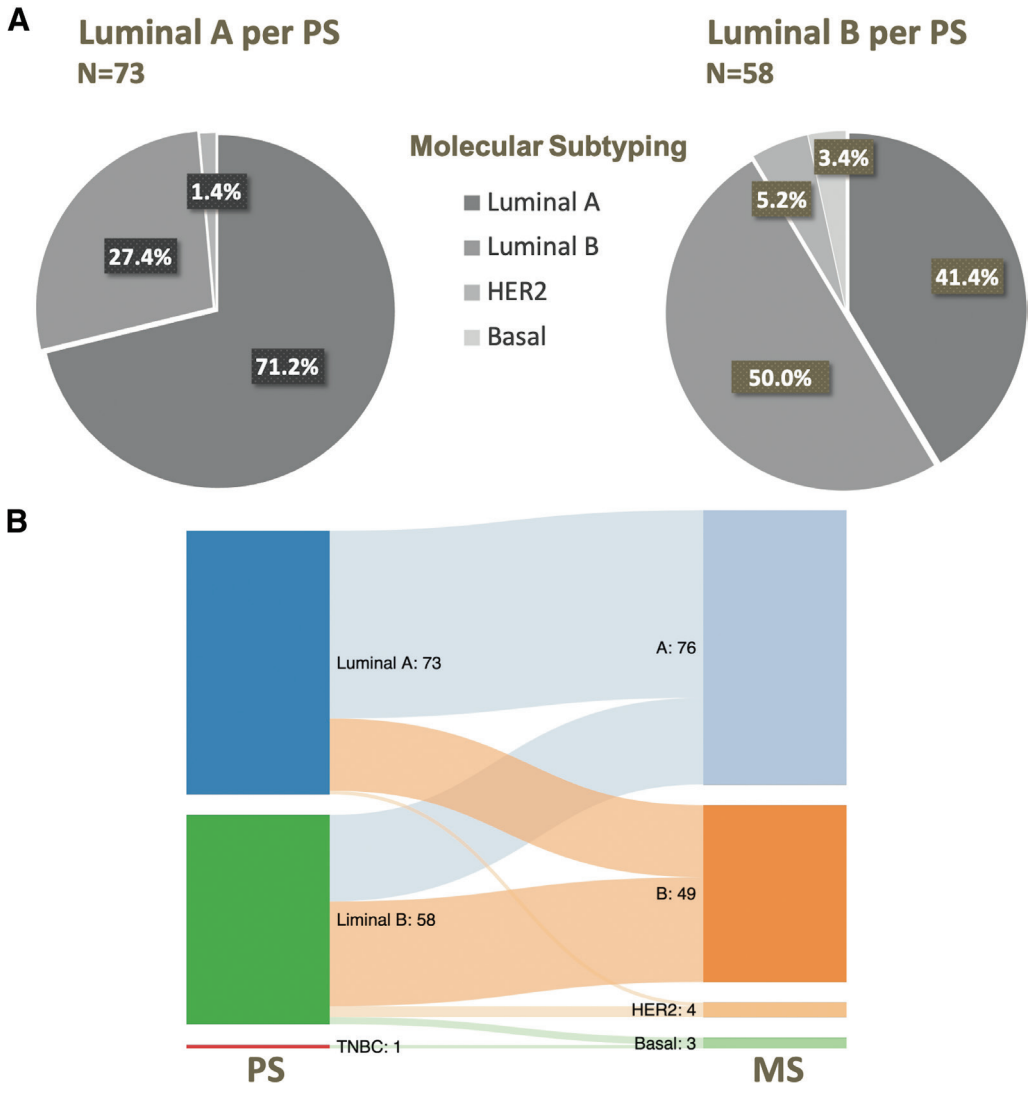

Fig. 1 Comparison of concordance between MS and PS: (A) left: Distributions of intrinsic subtypes after MS interpretation in luminal A subtype per PS; (B) alluvial plot showing subtype switching between PS and MS. HER = human epidermal growth factor receptor; MS = molecular subtyping; PS = pathological subtyping.

Table 4

IHC-based prognosis models

	Molecular subtyping			MammaPrint	
Models[12]	LumA (n = 75)	LumB (n = 47)	*p*	Pearson r	*p*
IHC4[a]				−0.362	<0.001
Low risk	31 (81.6%)	7 (18.4%)	0.001		
Intermediate risk	42 (57.3%)	32 (42.7%)			
High risk	2 (20%)	8 (80%)			
IHC4-Ki67x4[b]				−0.361	<0.001
Low risk	51(69.9%)	22(30.1%)	0.02		
Intermediate risk	24(49.0%)	25(51.0%)			
High risk	0	0			
IHC4 VGH cutoff[c]				−0.382	<0.001
Low risk	37 (78.7%)	10 (21.3%)	<0.001		
Intermediate risk	37 (56.9%)	28 (43.1%)			
High risk	1 (10%)	9 (90%)			

ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemical; LumA = luminal A; LumB = luminal B; PgR = progesterone receptor; VGH = Veterans General Hospital.

[a]IHC4 = 94.7 ×[−0.100 ER10 − 0.079 PgR10 + 0.586 HER2 + 0.240 ln(1 + 10 × Ki67)].

[b]IHC4-Ki67x4 = 94.7 × [−0.100 ER10 − 0.079 PgR10 + 0.586 HER2 + 0.240 ln(1 + 4 × Ki67)].

[c]IHC4 VGH cutoff = 94.7 × [−0.1 × (ER percentage × ER intensity)/30 − 0.079 × PR percentage/10 + 0.586 × HER2 + 0.24 × ln(1 + 10 × Ki67)].

apply multigene assay in clinical practice. Our study disclosed a real-world perspective on how MS changed the clinical behavior and decision-making. Although patients who had multigene assay only account for a small part of our database, the study may be the largest one reported in Taiwan and represents the real-world data of multigene testing in our society. After a period of follow-up, we would like to review the correlation among results of multigene assay and the impact on decision-making of treatment. This study will provide information on precision medicine and may have impacts on policy of reimbursement in Taiwan.

Patients with ER-positive breast cancers tend to have better outcome than those with ER-negative tumors. Evidence stands that 5-year survival after diagnosis is about 10% superior for women with ER-positive tumors.[17,18] However, luminal B subtype constitutes a group of heterogeneous diseases and tends to have more unfavorable prognosis than luminal A breast cancer. Notably, Kennecke et al[19] proposed that luminal B tumors attained equivalent cumulative incidence in distant relapse compared with that of basal tumors at 15 years. It is crucial to identify such high-risk groups in ER-positive breast cancer to introduce more aggressive treatment. However, chemotherapy was often introduced in cases of positive lymph nodes even with favorable biologic behaviors, such as strong positivity for ER. MIDACT trial demonstrated that 46% of patients at high clinical risk might not require chemotherapy and present comparable survival outcome.[6] Based on current evidence, our institute recommended multigene assays such as Oncotype DX or MammaPrint/BluePrint testing only in ER-positive tumors. Nearly all patients in this study had ER-positive tumors, and most of them (82.3%, n = 107) presented strongly IHC results >90% for ER. The only one patient with ER-negative tumor (TNBC) had multiple underlying diseases, such as arrhythmia post-pacemaker implant, infectious endocarditis, and myocardial ischemia. We sent multigene assay under the concern of high risk from chemotherapy, but the result was still confirmed as a basal type. Meanwhile, none of the patients in our study harbored more than four positive lymph nodes, which represented our decision to apply multigene assays mainly in early breast cancer. Our study also demonstrated that most clinicopathological factors had no significance in relation to risk stratification or MS except tumor necrosis, LVI, and grade. These prognostic factors may reflect the tumor behavior that is associated with this RNA-processing 70-gene signatures.

Our study found a moderate correlation between IHC4 and MS. It indicated that the complex gene signatures were not easily replaced by local laboratory testing. However, IHC4 can still be surrogate for patients who cannot afford the expense of multigene assays. Previous study of our team had observed that after adjustment of the cutoff values using the results of multigene

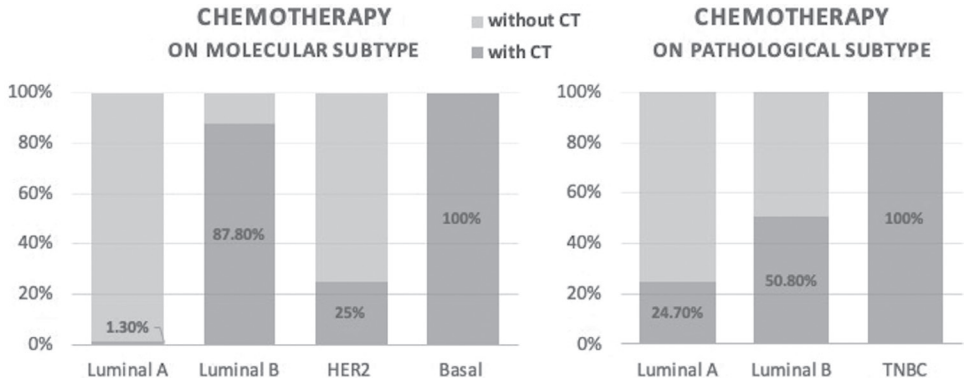

Fig. 2 Chemotherapy for patients with different subtypes according to MS or PS. CT = chemotherapy; HER = human epidermal growth factor receptor; MS = molecular subtyping; PS = pathological subtyping.

assay, positive predictive values were >90% to estimate the low risk or low recurrence score (≤21). Therefore, when the risk estimated by IHC-based prognostic models showed clearly high or low, it may be reasonable to omit multigene assays.[13] Only those estimated as intermediate risk may further benefit from precise information provided by multigene assays. The clinical factors were also helpful to determine the indication of chemotherapy and had been proposed to be added as IHC4 + C scores to predict the risk of recurrence and help more patients spare from chemotherapy.[20]

Although various reviews of multigene assays had been published, studies that focus on the clinical impacts of MammaPrint/BluePrint are limited. The limitation of our study includes small volume of patients, lack of survival analysis, and retrospective review. In Taiwan, the standard biomarkers for IHC4 are supported by national health insurance. In addition, chemotherapy such as anthracycline for all breast cancers and taxanes for node-positive tumors is also covered by government. However, multigene assays that are currently available on the market are all at patients' own expense. For node-positive patients who can be covered for the payment of chemotherapy, many physicians may apply chemotherapy rather than convince the patients that they may be the low-risk group determined by MS. Many patients also have financial difficulty to afford the relatively high cost of multigene assays. Thus, we can only have a smaller series from ER-positive and operable early breast cancer. The other limitation of our study is the lack of survival data. ER-positive breast cancers mostly present excellent outcomes, especially in early stage. All patients were alive without evidence of recurrence before the data recruitment so that the treatment outcomes, such as distant metastasis free survival or overall survival, will be approached in the future.

In conclusion, MS restratified 41.4% of patients with a luminal B PS subtype to a low-risk luminal A-type group. MammaPrint/BluePrint testing provides an additional information to help patients and clinicians in decision-making, but the high expense limits its application. The surrogate IHC4 score, with moderate correlation to MS, also provides an alternative tool when cost is considered. ER-positive early breast cancer patients mostly have favorable outcome, and the recommendation for chemotherapy should be prudential based on precise molecular subtypes.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A127.

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