专家述评

The evolution of prognostic and predictive markers in breast cancer

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[**Abstract**] Breast cancer is the most frequent cause of cancer death in women living in less developed regions of the world, and the second leading cause of cancer death in women living in more well-developed regions of the world. Breast cancer treatment options continue to evolve, with multiple treatment modalities now available; however, finding reliable predictive and prognostic biomarkers that will aid in selecting the appropriate treatment for breast cancer patients who would most likely respond to a specific therapy is still a major challenge, and has been the focus of many research groups throughout the past few decades. In this review, we attempt to provide an overview of the current prognostic and predictive markers in breast cancer including traditional, immunohistochemical, and genomic assays, and assess the potential clinical use of these markers.

[**Key words**] Breast cancer; Prognosis; Prediction; Biomarkers; Evolution

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1 Introduction

Breast cancer is the most commonly diagnosed cancer worldwide in 2020 and the fifth leading cause of cancer mortality worldwide[1]. A growing understanding of the complex biology of breast cancer has shown that it is a diverse group of diseases that differ in histological features, clinical behavior, prognosis, transcriptional programming, and response to therapy[2].

The increased understanding of the biology of breast cancer has revolutionized the management of breast cancer, leading to more specific and personalized treatment protocols based on the biological characteristics of this disease. Still, only 2%-15% of patients who get chemotherapy based on the clinicopathologic features of the tumor benefit from it[3]. This has created the need for improved methodologies for prognosis (information on the likelihood of cancer progression in untreated patients) and prediction (information on the probability of therapy response) of breast cancer recurrence, and breast cancer response to treatment, respectively[4].

In the seminal paper by Perou et al[5], classification of breast cancer by molecular subtyping was classically described in 2000. In that study, a systematic investigation of gene expression patterns was done on thousands of human genes from different breast tumors in an effort to develop a methodology for classifying these tumors based on their gene expression patterns. That study resulted in the classification of breast cancers into five main subtypes, each of which showed distinct patterns of gene expression: 1) luminal A; 2) luminal B; 3) normal breast-like; 4) human epidermal growth factor receptor 2 (HER2) enriched; and 5) basal-like subtypes. Each subtype differed in incidence, patterns of recurrence, survival, and response to therapy[6] (Table 1).

Table 1 Intrinsic molecular subtypes of invasive breast cancer: biologic and clinical features (reproduced from reference[7])

Tumor features	Molecular subtypes			
	Luminal A	Luminal B	HER2 enriched	Basal-like
Patient's characteristics	Older Detected on screening	Younger	Younger Asian	Younger African American Hispanic BRCA1 carriers
Percentage	About 55%	About 15%	12%-18%	10%-15%
Histologic grade	Grade 1 or 2	Grade 2 or 3	Grade 2 or 3	Usually grade 3
Breast cancer types	Tubular Cribriform Papillary Mucinous Classic lobular	Invasive carcinoma, no special type	Invasive carcinoma, no special type, apocrine carcinoma	Medullary Secretory Adenoid cystic Metaplastic
Lymph-vascular invasion	About 30%	About 50%	About 50%	About 40%
>4 positive lymph nodes	About 10%	About 20%	About 30%	About 15%
Estrogen receptor	Positive: high expression	Positive: may be low expression	Typically negative	Negative
Progesterone receptor	Usually positive	May be low expression or negative	Typically negative	Negative
HER2	Negative	30%-50% positive	Positive	Negative
Ki-67 proliferative index	Low (<10%)	Typically high (>14%)	High (>20%)	Typically very high (>50%)
Prognosis	Favorable, possible late recurrence	Less favorable (more aggressive)	Unfavorable (improved with HER2-targeted therapy)	Unfavorable (subset shows good response to chemotherapy)
Time to recurrence	Late recurrence (may be >10 years)	Earlier recurrence	Usually short (5-10 years)	Usually short (<5 years)
Systemic therapy	Benefit from hormonal therapy Benefit from chemotherapy less clear	May see most benefit from both hormonal and chemotherapy	Significant benefit from HER2-targeted therapy + chemotherapy	Subset benefit from chemotherapy

In this review, we discuss the traditional pathologic markers and several multigene expression based assays, and their evolving role as predictive and prognostic markers in the treatment planning for breast cancer patients. Furthermore, we provide a practical step-wise approach to risk assessment in breast cancer patients as it applies to

therapeutic decision making and treatment planning.

2 Traditional prognostic markers

2.1 Lymph node status

The single most important traditional prognostic marker for breast cancer is the lymph node status. Similar to other carcinomas, metastatic breast cancer is thought to progress through several stages. For breast cancer, these stages may include a progression from atypical hyperplasia, to intraductal carcinoma, to local invasion, followed by metastasis to the lymph nodes and/or distant sites[8-9]. A direct relationship exists between the number of involved lymph nodes and the risk of metastasis. Some studies[10-12] have shown that as the number of involved lymph nodes increased, the survival status decreased, regardless of tumor size.

Staging of the axilla has always played a central role in the treatment of breast cancer, as axillary lymph nodes have long been recognized as a route for breast cancer to spread systemically. The ACOSOG Z0011 (Alliance) randomized clinical trial showed that among women with low-stage breast cancer, who 1) did not have palpable axillary adenopathy and, 2) had <3 sentinel lymph nodes containing metastases, the 10-year overall survival for patients treated with sentinel lymph node biopsy alone was non-inferior to those treated with axillary lymph node dissection[13]. As a result, targeted sentinel lymph node excision has become the standard of care, resulting in a reduction of the incidence and complications of axillary lymph node dissection.

2.2 Tumor size

The size of the primary tumor is one of the most important factors following the nodal status for decision making on adjuvant treatment. As with lymph node status, tumor size reflects the patient's tumor burden, and has also been found to act as an independent prognostic indicator. As tumor size increases, survival decreases regardless of lymph node status. Carter et al[10] reported that with tumors <1 cm, the 5-year overall survival was close to 100%, compared to 89% for patients with a tumor size between 1 cm and 3 cm, and 86% for patients with a tumor size between 3 cm and 5 cm. It is also thought that the risk of developing metastases increases with tumor size, as the larger the cancer is at diagnosis (reflecting a higher tumor burden), the more cells are available to metastasize[14]. As a result, detection of smaller, early stage tumors can substantially reduce the likelihood of metastatic spread. Primary tumor size can be measured by imaging, or more accurately evaluated after surgical excision.

2.3 Histologic features

Histologic grade is another widely used parameter that helps in determining the prognosis in patients with invasive breast cancer[15]. Low-grade tumors have a more favorable prognosis, and high-grade tumors have a less favorable prognosis. The Nottingham grading system is a grading system for invasive breast cancer that results in a combined score based on three histologic factors: tubular formation, nuclear pleomorphism, and mitotic index[16]. Each of these histologic factors is assigned a score from 1 to 3, with 1 being consistent with a lower histologic grade, and 3 being consistent with a higher histologic grade. These scores are then added together. If the combined Nottingham tumor score is between 3 and 5, the tumor is assigned a Nottingham grade of 1, consistent with a well differentiated tumor and a more favorable prognosis. If the combined Nottingham tumor score is 8 or 9, it is assigned a Nottingham grade of 3, consistent with a poorly differentiated tumor and a less favorable prognosis. If the combined Nottingham tumor score is 6 or 7, it is assigned a Nottingham grade of 2, suggesting a prognosis between that of a Nottingham grade 1 and 3[17-18]. In 2017, the Nottingham grading system was incorporated into the American Joint Committee on Cancer (AJCC) for breast cancer staging[19]. When strict diagnostic criteria are applied, it has been shown that lower grade histologic subtypes of breast cancer and certain specific histologic subtypes, such as tubular carcinoma and mucinous carcinoma, have a more favorable prognosis when compared to higher grade histologic subtypes[20-21].

2.4 Immunohistochemical stains

The role of immunohistochemical stains (IHC) has increased dramatically in recent years and became a critical part of the routine workup for breast cancer. Different institutions use different sets of routine IHCs; however, the most characteristically used markers are estrogen receptor (ER), progesterone receptor (PR), and HER2. The positive or negative expressions of these three markers

define the four different breast cancer subtypes: luminal A, luminal B, HER2 enriched, and triple negative(TN)[22]. Each breast cancer subtype has a different prognosis, with different implications for chemotherapeutic options. As such ER, PR, and HER2 provide prognostic and predictive information for the currently available anti-hormonal and anti-HER2 therapies.

Generally, ER expressing breast cancers are better differentiated, and have indolent behavior, a better prognosis, and are eligible for anti-estrogen hormonal therapy[23]. Even tumors with very low levels of ER expression have the potential to benefit from hormonal therapy. In addition to ER, PR is also a routinely tested transcription factor, and is largely regulated by ER. Both ER and PR markers are expressed in a large subset of breast cancers. Even though some studies suggest that the role of PR may not be as useful clinically as ER[24], multiple studies suggested that the loss of PR expression in ER-positive tumors is associated with a worse prognosis, a more aggressive clinical course, and decreased response to tamoxifen therapy[25-26]. The American Society of Clinical Oncology/College of American Pathologists(ASCO/CAP) guidelines recommend that ER and PR should be considered positive if $\geqslant 1\%$ of tumor cells show nuclear staining of any intensity[27].

HER2 belongs to a family of transmembrane tyrosine kinase receptors that plays an important role in the regulation of cellular signaling that affects cell growth, differentiation, and survival[28]. HER2/neu gene amplification and/or protein overexpression has been identified in 15%-20% of invasive breast cancers[29]. Studies have shown that HER2 enriched breast cancer is associated with an aggressive clinical course and poor outcome[30]. The role of HER2 and its biology has been extensively studied, leading to the development of the drug trastuzumab, a humanized monoclonal antibody that directly targets the HER2 receptor. Trastuzumab has become an important therapeutic option for patients with HER2 positive breast cancer[31]. The success and evidence based clinical benefit of trastuzumab was followed by expanding the horizon for other HER2 targeted agents, including the humanized monoclonal antibody pertuzumab[32], tyrosine kinase inhibitors(lapatinib, neratinib, tucatinib)[33] and the antibody-drug conjugated ado-trastuzumab emtansine, which had shown improved outcomes in patients with HER2-positive early breast cancer who had residual invasive disease after completion of neoadjuvant therapy[34].

HER2 protein expression can be detected by IHC, while *HER2* gene amplification can be identified by *in-situ* hybridization (ISH), most commonly fluorescent in-situ hybridization(FISH). Initial evaluation of HER2 by IHC has been widely-used due to its availability and low cost, and the equivocal case will be automatically reflexed to ISH testing. The evaluation of HER2 expression by immunohistochemistry in breast cancer is semi-quantitative rather than qualitative, since a background level of up to 20,000 HER2 receptor molecules is expressed in all breast epithelial cells[30]. Based on the intensity of the stain and the membranous staining pattern, tumors are classified as negative(scored as 0 or 1+), equivocal (2+) or positive(3+)[35].

In addition to the aforementioned markers, Ki-67 is another immunohistochemical stain that has been shown to be helpful for distinguishing breast cancers at a higher risk for recurrence[36]. Several studies have shown that Ki-67 has an independent predictive and prognostic value in terms of response to endocrine therapy and chemotherapy, as well as overall survival in breast cancer patients[37]. In a study that included 1951 cases of primary breast cancers, it was found that triple negative breast cancers showed the highest Ki-67 index[mean $(50.9 \pm 23.7)\%$], followed by HER2/neu[mean $(42.6 \pm 21.6)\%$] and luminal B cancers[mean $(34.9 \pm 20.05)\%$], while luminal A cancers showed lowest Ki-67 index[mean $(23.6 \pm 19.7)\%$][38]. However, the use of Ki-67 in routine clinical practice in breast cancer remains controversial due to the lack of a standardized procedure for Ki-67 assessment, and the persistence of several issues of debate with regards to the Ki-67 assay interpretation and the lack of a validated cut-off point[39].

2.5 Genomic tests

The introduction of genomic testing into the clinical practice has changed the approach of how breast cancer patients are evaluated for risk of recurrence and treatment alternatives. In addition to the conventional pathologic factors and biomarkers used for assessing tumor behavior, several multigene expression-based assays that offer prognostic and predictive information for risk of recur-

rence and treatment efficacy have become established and commercially available over the past several years.

Multigene expression-based assays differ in the technological platforms used to measure gene expression, the number and identity of assessed genes, and the patient populations used for clinical validation. Here we discuss the more commonly used multigene expression-based assays (Table 2).

Table 2 Commercially available molecular profiling tests for prognostication in ER positive breast cancer (reproduced from reference[40])

							Recommended use to guide decisions about adjuvant systemic therapy	
Test	Material	Method	Component genes	Validation	Molecular subtyping	Stratification of recurrence risk	ASCO	NCCN *
Oncotype DX (Genomic Health, Redwood City, CA, USA)	FFPE	RT-PCR	21 genes	ER +, HER2 – 0-3 positive nodes	No	Low Intermediate High	ER +, HER2 –, and node negative	ER +, HER2 –, and node negative or positive **
MammaPrint (Agendia, Amsterdam, The Netherlands)	Fresh FFPE	Microarray	70 genes	ER +/–, HER2 – Stage 1-2 0-3 positive nodes	Yes	Low High	ER +, HER2 –, and node negative or positive, high clinical risk only	ER +, HER2 – and node negative or positive ** high clinical risk only
Prosigna (NanoString Technologies Inc. Seattle, WA, USA)	FFPE	RT-PCR	46 genes ***	ER +, HER2 – Stage 1-2 0-3 positive nodes	Yes	Node negative: Low Intermediate High Node positive: Low High	ER +, HER2 –, and node negative, in conjunction with other clinical and pathologic variables	ER +, HER2 –, and node negative or positive **
EndoPredict (Sividon Diagnostics GmbH, Koln, Germany)	FFPE	RT-PCR	12 genes	ER +, HER2 – 0-3 positive nodes	No	Low High	ER +, HER2 –, and node negative	ER +, HER2 –, and node negative or positive **
Breast Cancer Index (Biotheranostic, San Diego, CA, USA)	FFPE	RT-PCR	Combine 2 independent biomarkers (HOXB13:IL17BR) into a ratio[H/I], and a 5-gene molecular grade index(MGI)	ER/PR +, HER2 – 0-3 positive nodes	No	Prognostic score ****: Low High Predictive score *****: Low High	ER +, HER2 –, and node negative	ER +, HER2 –, and node negative

Note: Abbreviations: AJCC:American Joint Committee on Cancer; ASCO: American Society of Clinical Oncology; ER: estrogen receptor; FFPE: formalin-fixed paraffin-embedded; HER2:human epidermal growth factor receptor 2; NCCN:National Comprehensive Cancer Network; RS: recurrence score; RT-PCR:reverse transcription polymerase chain reaction

* The NCCN prefers the use of Oncotype Dx for prognosis and prediction of chemotherapy benefit, and recommends only Oncotype Dx for use of prediction of chemotherapy benefit.

** The NCCN recommends that multigene assay testing in lymph node positive patients only be considered in patients who are already designated as potential candidates for systemic adjuvant chemotherapy based on clinical characteristics, tumor stage and pathology.

** Originally Prosigna had 50 discriminator genes; however, it was found that four of those genes did not add any prognostic value.

*** Likelihood of recurrence

**** Likelihood of benefit from extended endocrine therapy

2.6 Oncotype DX

Oncotype DX (ODX) is a quantitative real-time reverse transcriptase polymerase chain reaction (qRT-PCR) mRNA-based multigene assay developed through collaborations between Genomic Health Incorporated and the National Surgical Adjuvant Breast and Bowel Project (NSABP). It is performed on RNA extracted from formalin-fixed paraffin-embedded (FFPE) breast cancer tissue samples that are ER-positive and lymph node-negative[41]. The development of the ODX assay depended mainly on cohort studies with long-term follow-up of patients with early breast cancer[41-42]. The assay evaluates mRNA from 21 genes, among which 16 are cancer-related genes, and 5 reference genes used to check RNA integrity and to normalize expression levels. The evaluated 16 cancer-related genes are heavily influenced by proliferation-related genes, hormone receptor-related genes, and HER2-related genes[41]. An algorithm is used to calculate an ODX recurrence score (ODXRS) that ranges from 0 to 100, reported as either low risk (< 18), intermediate risk (18-30), or high risk (> 30). The ODX assay is validated for predicting the risk of breast cancer recurrence at 10 years[41], and for predicting benefit from adjuvant chemotherapy in ER positive lymph node negative breast

cancer[41,43-45]. The TAILORx results suggest that an ODXRS of less than 11 has an extremely low risk of developing recurrence, and that women with early breast cancer who are older than 50 years with an ODXRS <26 have a similar risk to patients in the lower risk ODX category[46]. The ODXRS provides a more accurate and reproducible measure of breast cancer risk of recurrence and therapeutic effectiveness than the standard evaluation of histologic variables alone.

2.7 MammaPrint and BluePrint

MammaPrint (MP) is a genomic assay that uses microarray technology to measure the expression of 70 genes that are involved in cell cycle and proliferation, invasion and metastasis, angiogenesis, and signal transduction[47]. This assay is marketed by Agendia, BV (Amsterdam, Netherlands). Its main use is as prognostic marker for risk of distant recurrence at 5 years. MammaPrint classifies patients into two risk groups: low risk, with a 1.3% risk of distant recurrence at 5 years, and high risk, with an 11.7% risk of distant recurrence at 5 years. Test validation of MP was performed in a study that included 295 breast cancers with available banked, fresh-frozen tissue from Netherlands Cancer Institute, including patients with and without lymph node involvement[48]. Results showed significantly different outcomes for patients with low-risk signatures (14.8% 10-year distant recurrence) vs high-risk signatures (50% 10-year distant recurrence). Interestingly, poor prognosis correlated with the traditional high-risk pathologic factors such as increased tumor size and high histologic grade.

The clinical benefit of MP was recently validated in a prospective randomized trial, the MINDACT trial[49]. This was a randomized phase Ⅲ study, which enrolled more than 6,600 patients with breast cancer who were ER positive and HER2 negative, ER positive and HER2 positive, ER negative and HER2 positive, or triple negative. Patients had MP performed to determine genomic risk, while clinical risk was determined by using Adjuvant! Online[50-51] (the modified version 8.0 with HER2 status). The study included only patients with discordant genomic and clinical risk assessments. Patients were randomized to chemotherapy vs no chemotherapy. Results showed that patients classified as low risk by MP but at high risk based on clinical risk had an excellent outcome, with a 5-year distant metastasis-free survival of 94.7%. In these clinically high risk patients, the use of MP rather than the traditional criteria resulted in a 46% reduction in the use of adjuvant chemotherapy. Over all, when MP was used rather than the traditional criteria, there was a 14% reduction in the use of adjuvant chemotherapy. This study resulted in guideline recommendations by ASCO, suggesting that if a breast cancer patient is clinically high risk with a low risk MP, then MP may be used to inform decision to withhold adjuvant chemotherapy[52]. ASCO does not recommend using MP in breast cancer patients who are clinically low risk[52].

BluePrint (BP), an 80-gene breast cancer molecular subtyping microarray-based test also marketed by Agendia that was developed using an IHC-based clinical subtype as a guide[53]. The BP assay measures the expression of 80 genes that assess functional pathways which determine the intrinsic breast cancer molecular subtypes by measuring the similarity of the tested tumor to a representative profile luminal-type (58 genes), basal-type (28 genes), and HER2-type (4 genes)[54]. For each tested tumor, the similarity to all three representative profiles is calculated and the subtype with the greatest magnitude is determined to be the breast cancer molecular subtypes[54]. When BP is combined with MP, breast cancers can be classified into a luminal A signature (low risk), a luminal B (high risk), a HER2 signature, and a basal-type signature. Studies have shown that tumors of different BP signatures exhibit differences in long term survival and response to neoadjuvant therapy. Tumors with luminal-type BP signature have more favorable distant metastasis (DM) free survival but less pathological complete response to neoadjuvant therapy, whereas tumors with basal-type BP signature and HER-type BP signature tumors have less favorable DM free survival but are more sensitive to chemotherapy[53,55].

2.8 Prosigna

Prosigna is a second-generation multigene expression assay, comprised of 50 discriminator genes and 8 controls, popularly known as the Prediction Analysis of Microarray 50 (PAM50) gene signature[56]. This test has been cleared by the United States Food and Drug Administration (US-FDA) for postmenopausal patients with ER positive cancer, who have undergone treatment, and only

receive adjuvant endocrine therapy[5]. The assay is marketed by Prosigna(NanoString Technologies, Seattle,WA). Originally it comprised of 50 discriminator genes and 8 controls; however, it was found that four of those genes did not add any prognostic value, so a 46-gene expression profile is used to assign cancers to four PAM50 molecular subtypes: luminal A, luminal B, HER2 enriched, and basal-like. An 18-gene subset of the 46-gene panel is used to calculate a proliferation score, which in combination with the molecular profile and the pathologic tumor size determines the 10-year Prosigna risk of recurrence(ROR) score[57]. For lymph node negative patients, the ROR is classified as low risk(<5%, scores 0-40), intermediate risk(about 10%, scores 41-60), and high risk (>15%, scores 61-100). For lymph node positive patients, the ROR is classified as low risk(about 5%, scores 0-40) and high risk(about 25%, scores 41-100)[58]. Including the tumor size, the ROR risk strengthens the Prosigna test as a prognostic assay; however, the predictive value of this assay has not been widely tested.

3 Using IHC as a prognostic and predictive tool

Genomic testing is expensive, and not available to certain patients, particularly patients in less developed countries around the world. The list price reported in the Genomic Health 2017 Annual Report for the invasive breast carcinoma ODX test was $4,620[59-60]. Many of the previously discussed genomic assays measure similar variables assessed in the traditional pathologic evaluation of breast carcinoma, including tumor proliferation, tumor grade, and IHC for ER, PR, and HER2. As such, an alternative approach for risk-stratifying breast cancer is to use IHC-based markers for clinical testing, and it has been suggested that IHC can be used independently for subtyping breast cancer, as well as risk stratifying certain types of breast cancer patients[61-63].

Immunohistochemical markers such as ER,PR,HER2, and Ki-67 have showed great promise for risk-stratifying breast cancer patients into groups similar to subtypes that have been defined by gene expression studies[64-66]. The use of certain immunohistochemistry antibody panels for routine pathologic evaluation of newly diagnosed breast cancer patients might provide useful information for guiding clinical decisions about adjuvant therapies rapidly and cost-effectively; however, antibody panels must be validated rigorously using multiple patient cohorts from multiple institutions to define their practicality and clinical utility before entering routine clinical practice[64], as lack of reproducibility and reliability due to poor assay standardization is a concern[67].

Several national quality assurance programs have created guidelines to include standardization of pre-analytical, analytical, and post-analytical testing factors, as well as mandatory proficiency testing, resulting in improvement in the quality, reliability, and inter-laboratory agreement for breast cancer assays[68-72]. This has made the use of antibody panels results more feasible for predicting breast cancer risk. Below we discuss three of the more commonly known immunohistochemistry antibody panel assays and techniques used for predicting breast cancer risk of recurrence.

3.1 Mammostrat® immunohistochemistry-based multiplex assay

Mammostrat®(GE/Clarient, Aliso Viejo, CA), is an IHC assay that measures the expression of five proteins(p53, HTF9C, CEACAM5, nDRG1, and SLC7A5) in ER positive, lymph node negative, HER2 negative breast cancers. These five proteins are believed to be associated with risk of breast cancer recurrence[73-74]. Mammostrat® was developed in a predominantly post-menopausal cohort, and has been suggested for use in older patients with newly diagnosed, early stage breast cancer[75]. The expression levels of the five proteins are translated into a risk index classifying patients into low, moderate, or high risk for recurrence over 10 years. Mammostrat® has been validated using three independent institutional cohorts of patients[74], as well as using archival tissue samples from the NSABP B14 and B20 clinical trials. Bartlett et al[73,76] have also confirmed the efficacy and prognostic significance of Mammostrat® in a validation study of 3,837 cases from tamoxifen or exemestane treated node-positive or node-negative patients who were enrolled in the Tamoxifen Exemestane Adjuvant Multinational(TEAM) trial. Acs et al[77] have suggested that Mammostrat® may provide a better estimation of tumor behavior in certain subgroups of low-grade breast carcinomas. Murray et al[78] have suggested that this benefit is time-dependent, and most prognostic over the first five years of follow-up, with an ability to potentially predict early recurrence during

this time period. Mislick et al[79] have suggested that Mammostrat® costs savings for women with early-stage breast cancer compared to ODX.

Mammostrat®, is currently considered investigational and/or experimental and is not generally accepted as standard of care in the evaluation or management of breast cancer patients.

3.2 IHC4 score

The IHC4 score was developed in 2011 at the Wolfson Institute of Preventative Medicine, London, UK on patients included in the translational arm of the retrospective cohort from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial of ER-positive breast cancer patients[80]. The IHC4 assay is performed on FFPE tissue and uses the immunohistochemical assessment of ER, PR, Ki-67, and HER2 to calculate a risk score using weighting factors and an algorithm. The assay was validated and found to be prognostic in a cohort of 786 breast cancer patients, both pre- menopausal and post-menopausal status, none of whom received adjuvant therapy[81-82], and has been reported to have prognostic utility similar to the ODX recurrence score[80]. A recent study suggested that the IHC4 score was predictive of pathologic response following neoadjuvant chemotherapy[83-84]. Investigators combined the IHC4 score with clinical and pathologic variables including the involvement of regional lymph nodes, size and extent of the primary tumor, histologic grade, and patient age to create an IHC4+ C score[85], which improved the prognostic accuracy of the IHC4 score. Recent studies have further validated the use of the IHC4+ C score for identifying patients at low risk who potentially can avoid adjuvant radiotherapy[86].

It is unclear how the IHC4 and IHC4+ C scores might perform with decentralized testing, given the interobserver and interlaboratory variability of semi-quantitative IHC testing. As such, the IHC4 and IHC4+ C scores should be considered investigational until additional prospective studies are done to further evaluate their interobserver and interlaboratory variability.

3.3 Magee equations

The recent literature[59,64,87-92] suggests that algorithms and models that use ranges of ER, PR, HER2 and Ki-67 results can provide information similar to that from multigene assays with significant cost savings[65]. In 2008, Flanagan et al[87] published a linear equation (the original Magee equation) using different combinations of standard histopathologic variables, including the mitotic index, ER H-score, PR H-score, HER2, Ki-67, and tumor size, to calculate a recurrence score, which was shown to correlate well with the ODX recurrence score. In 2013, Klein et al[90] revised the original Magee equation, publishing three new linear equations(the new Magee equations), using the Nottingham score, ER H-score, PR H-score, HER2, Ki-67, and tumor size. These new Magee equations also calculated a recurrence score, which also was shown to correlate well with the ODX recurrence score. In 2015, Turner et al[91] published a modification of these new Magee equations, using a modification of the H-score, making it easier to use the equations(the modified Magee equations). These modified Magee equations were shown to correlate well with the ODX recurrence score, and were published with an algorithmic approach using an average modified Magee score supporting a "stepwise" risk stratification approach, with the omission of ODX testing in certain breast cancer patients, and the reflex of ODX testing in others. An algorithmic approach using the Magee equations published by Bhargava et al[93-94] also supports the potential for this "stepwise" risk stratification approach. Several other studies have reinforced that the use of the Magee equations can be helpful in predicting patients likely to have either a low or high ODX score, with the suggestion that it may be reasonable to omit multigene assays in certain situations, particularly when the cost is a consideration[95-99]. Turner et al[59] subsequently validated the 2015 modified Magee algorithmic approach, publishing the Rochester Modified Magee algorithm(RoMMa) in a multi-institutional study, with outcome data showing that only 2.0% of patients classified as low risk by the RoMMa had a breast cancer recurrence over 5-10 years of follow-up.

The Magee equations have also been suggested to be predictive for pathologic response to neoadjuvant chemotherapy[100-101] and to be predictive for distal metastatic risk in male breast cancer patients[102].

It is unclear how the Magee score might perform with decentralized testing, given the interobserver and interlaboratory variability of semi-quantitative IHC testing. As such, the Magee score should be considered

investigational until additional prospective studies are done to further evaluate their interobserver and interlaboratory variability.

4 Summary

The new paradigms of pathologic diagnostic testing for breast cancer patients continue to evolve with the increased importance of personalized patient care. As multigene assay testing continues to offer improvements on current practice, the traditional clinical-pathologic paradigm provides a complement to this next-generation of testing, in an effort towards providing cost-effective, and cost-efficient medical care for breast cancer patients. A practical "stepwise" approach when risk-stratifying breast cancer patients might be to use information from the traditional clinical-pathologic paradigm to help identify patients with clinical and pathological metrics that will likely elicit information that is similar to multigene assay testing. In these cases, multigene assay testing may not provide any additional significant clinical utility, and would likely not be cost-effective or cost-efficient. Multigene assay testing could then be limited to cases where the assay results would potentially provide clinical utility beyond the available clinical and pathologic metrics. The potential cost savings to the health-care system would be significant. The successful integration of the traditional clinical-pathologic paradigm into these new paradigms of pathologic diagnostic testing will depend on the reproducibility of interobserver and interlaboratory results in both centralized and decentralized laboratory settings.

As new prognostic and predictive models emerge over the next several years, both the traditional clinical-pathologic paradigm and the next generation of multigene assay development will continue to evolve. New prognostic and predictive models include the use of nontraditional biomarkers, miRNA-based signatures, predictive algorithms, predictive nomograms, and predictive models based on the microenvironment of the tumor[64]. As prognostic and predictive models arrive on the scene, attention must be paid to the validity of prognostic and predictive modeling in diverse ethnic populations, because it is not clear how differences in ethnicity affect the outcomes predicted by the currently used prognostic and predictive models[64]. With these things in mind, the future of prognostic and predictive testing for breast cancer patients seems bright.

References

[1] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin, 2021,71(3):209 - 249.

[2] Reis-Filho JS, Pusztai L. Gene expression profiling in breast cancer: classification, prognostication, and prediction[J]. Lancet, 2011,378(9805):1812 - 1823.

[3] Early Breast Cancer Trialists' Collaborative Group(EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials[J]. Lancet, 2005,365(9472):1687 - 1717.

[4] Weigelt B, Reis-Filho JS, Swanton C. Genomic analyses to select patients for adjuvant chemotherapy: trials and tribulations[J]. Ann Oncol, 2012,23 Suppl 10:x211 - x218.

[5] Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours[J]. Nature, 2000,406(6797): 747 - 752.

[6] Hu Z, Fan C, Oh DS, et al. The molecular portraits of breast tumors are conserved across microarray platforms[J]. BMC Genomics, 2006, 7:96.

[7] Lester SC, Hicks DG. Diagnostic Pathology: Breast. Vol[M]. 3rd Edition. Elsevier, 2021:784.

[8] Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited[J]. Nat Rev Cancer, 2003,3(6):453 - 458.

[9] Weigelt B, Peterse JL, van't Veer LJ. Breast cancer metastasis: markers and models[J]. Nat Rev Cancer, 2005,5(8):591 - 602.

[10] Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases[J]. Cancer, 1989, 63(1):181 - 187.

[11] Fisher B, Bauer M, Wickerham DL, et al. Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer[J]. An NSABP update. Cancer, 1983,52(9):1551 - 1557.

[12] Fung F, Cornacchi SD, Vanniyasingam T, et al. Predictors of 5-year local, regional, and distant recurrent events in a population-based cohort of breast cancer patients[J]. Am J Surg, 2017,213(2): 418 - 425.

[13] Giuliano AE, Ballman KV, McCall L, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) randomized clinical trial[J]. JAMA, 2017,318(10):918 - 926.

[14] Sivaramakrishna R, Gordon R. Detection of breast cancer at a smaller size can reduce the likelihood of metastatic spread: a quantitative analysis[J]. Acad Radiol, 1997,4(1):8 - 12.

[15] Dunnwald LK, Rossing MA, Li CI. Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients[J]. Breast Cancer Res, 2007,9(1):R6.

[16] Bloom HJ, Richardson WW. Histological grading and prognosis in breast cancer; a study of 1409 cases of which 359 have been followed for 15 years[J]. Br J Cancer,1957,11(3):359 - 377.

[17] Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up[J]. Histopathology, 1991, 19(5):403 - 410.
[18] Elston EW, Ellis IO. Method for grading breast cancer[J]. J Clin Pathol, 1993,46(2):189 - 190.
[19] Giuliano AE, Connolly JL, Edge SB, et al. Breast cancer—major changes in the American Joint Committee on Cancer eighth edition cancer staging manual[J]. CA Cancer J Clin, 2017,67(4):290 - 303.
[20] Carstens PH, Greenberg RA, Francis D, et al. Tubular carcinoma of the breast. A long term follow-up[J]. Histopathology, 1985,9(3): 271 - 280.
[21] Clayton F. Pure mucinous carcinomas of breast: morphologic features and prognostic correlates[J]. Hum Pathol, 1986,17(1):34 - 38.
[22] Rakha EA, Reis-Filho JS, Ellis IO. Combinatorial biomarker expression in breast cancer[J]. Breast Cancer Res Treat, 2010,120(2): 293 - 308.
[23] Harvey JM, Clark GM, Osborne CK, et al. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer[J]. J Clin Oncol, 1999,17(5):1474 - 1481.
[24] Viale G, Regan MM, Maiorano E, et al. Prognostic and predictive value of centrally reviewed expression of estrogen and progesterone receptors in a randomized trial comparing letrozole and tamoxifen adjuvant therapy for postmenopausal early breast cancer: BIG 1-98[J]. J Clin Oncol, 2007,25(25):3846 - 3852.
[25] Cui X, Schiff R, Arpino G, et al. Biology of progesterone receptor loss in breast cancer and its implications for endocrine therapy[J]. J Clin Oncol, 2005,23(30):7721 - 7735.
[26] Rakha EA, El-Sayed ME, Green AR, et al. Biologic and clinical characteristics of breast cancer with single hormone receptor positive phenotype[J]. J Clin Oncol, 2007,25(30):4772 - 4778.
[27] Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer(unabridged version)[J]. Arch Pathol Lab Med, 2010,134(7):e48 - e72.
[28] Ross JS, Fletcher JA, Linette GP, et al. The HER-2/neu gene and protein in breast cancer 2003: biomarker and target of therapy[J]. Oncologist, 2003,8(4):307 - 325.
[29] Waks AG, Winer EP. Breast cancer treatment: a review[J]. JAMA, 2019,321(3):288 - 300.
[30] Ross JS, Fletcher JA, Bloom KJ, et al. HER-2/neu testing in breast cancer[J]. Am J Clin Pathol, 2003,120 Suppl:S53 - S71.
[31] Lane HA, Motoyama AB, Beuvink I, et al. Modulation of p27/Cdk2 complex formation through 4D5-mediated inhibition of HER2 receptor signaling[J]. Ann Oncol, 2001,12 Suppl 1:S21 - S22.
[32] Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer[J]. N Engl J Med, 2012, 366(2):109 - 119.
[33] Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer[J]. N Engl J Med, 2006, 355(26):2733 - 2743.
[34] von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer[J]. N Engl J Med, 2019,380(7):617 - 628.
[35] Ridolfi RL, Jamehdor MR, Arber JM. HER-2/neu testing in breast carcinoma: a combined immunohistochemical and fluorescence in situ hybridization approach[J]. Mod Pathol, 2000,13(8):866 - 873.
[36] Cheang MC, Chia SK, Voduc D, et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer[J]. J Natl Cancer Inst, 2009,101(10):736 - 750.
[37] Petrelli F, Viale G, Cabiddu M, et al. Prognostic value of different cut-off levels of Ki-67 in breast cancer: a systematic review and meta-analysis of 64,196 patients[J]. Breast Cancer Res Treat, 2015,153 (3):477 - 491.
[38] Hashmi AA, Hashmi KA, Irfan M, et al. Ki67 index in intrinsic breast cancer subtypes and its association with prognostic parameters[J]. BMC Res Notes, 2019,12(1):605.
[39] Penault-Llorca F, Radosevic-Robin N. Ki67 assessment in breast cancer: an update[J]. Pathology, 2017,49(2):166 - 171.
[40] Zhang H, Hicks DG. Breast and gynecologic tumors[A]. ed. D. Y. a. Z. L. Practical Oncologic Molecular Pathology: Frequently Asked Questions[M]. Springer, 2021.
[41] Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer[J]. N Engl J Med, 2004,351(27):2817 - 2826.
[42] Cobleigh MA, Tabesh B, Bitterman P, et al. Tumor gene expression and prognosis in breast cancer patients with 10 or more positive lymph nodes[J]. Clin Cancer Res, 2005,11(24 Pt 1):8623 - 8631.
[43] Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer[J]. J Clin Oncol, 2006,24(23):3726 - 3734.
[44] Toi M, Iwata H, Yamanaka T, et al. Clinical significance of the 21-gene signature(Oncotype DX) in hormone receptor-positive early stage primary breast cancer in the Japanese population[J]. Cancer, 2010, 116(13):3112 - 3118.
[45] Dowsett M, Cuzick J, Wale C, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study[J]. J Clin Oncol, 2010,28(11):1829 - 1834.
[46] Sparano JA, Gray RJ, Makower DF, et al. Clinical outcomes in early breast cancer with a high 21-gene recurrence score of 26 to 100 assigned to adjuvant chemotherapy plus endocrine therapy: a secondary analysis of the TAILORx randomized clinical trial[J]. JAMA Oncol, 2020, 6(3):367 - 374.
[47] Tian S, Roepman P, Van't Veer LJ, et al. Biological functions of the genes in the mammaprint breast cancer profile reflect the hallmarks of cancer[J]. Biomark Insights, 2010,5:129 - 138.
[48] van de Vijver MJ, He YD, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer[J]. N Engl J

Med, 2002,347(25):1999 – 2009.

[49] Audeh W, Blumencranz L, Kling H, et al. Prospective validation of a genomic assay in breast cancer: the 70-gene MammaPrint assay and the MINDACT trial[J]. Acta Med Acad, 2019,48(1):18 – 34.

[50] Mook S, Schmidt MK, Rutgers EJ, et al. Calibration and discriminatory accuracy of prognosis calculation for breast cancer with the online Adjuvant! program: a hospital-based retrospective cohort study[J]. Lancet Oncol, 2009,10(11):1070 – 1076.

[51] Olivotto IA, Bajdik CD, Ravdin PM, et al. Population-based validation of the prognostic model ADJUVANT! for early breast cancer [J]. J Clin Oncol, 2005,23(12):2716 – 2725.

[52] Henry NL, Somerfield MR, Abramson VG, et al. Role of patient and disease factors in adjuvant systemic therapy decision making for early-stage, operable breast cancer: update of the ASCO endorsement of the Cancer Care Ontario guideline[J]. J Clin Oncol, 2019, 37(22):1965 – 1977.

[53] Krijgsman O, Roepman P, Zwart W, et al. A diagnostic gene profile for molecular subtyping of breast cancer associated with treatment response[J]. Breast Cancer Res Treat, 2012,133(1):37 – 47.

[54] Mittempergher L,Delahaye LJ,Witteveen AT,et al. Performance characteristics of the BluePrint® Breast Cancer Diagnostic Test[J]. Transl Oncol, 2020,13(4):100756.

[55] Whitworth P, Stork-Sloots L, de Snoo FA, et al. Chemosensitivity predicted by BluePrint 80-gene functional subtype and MammaPrint in the Prospective Neoadjuvant Breast Registry Symphony Trial(NBRST) [J]. Ann Surg Oncol, 2014,21(10):3261 – 3267.

[56] Parker JS, Mullins M, Cheang MC, et al. Supervised risk predictor of breast cancer based on intrinsic subtypes[J]. J Clin Oncol, 2009, 27(8):1160 – 1167.

[57] Wallden B, Storhoff J, Nielsen T, et al. Development and verification of the PAM50-based Prosigna breast cancer gene signature assay [J]. BMC Med Genomics, 2015,8:54.

[58] Gnant M, Filipits M, Greil R, et al. Predicting distant recurrence in receptor-positive breast cancer patients with limited clinicopathological risk: using the PAM50 Risk of Recurrence score in 1478 postmenopausal patients of the ABCSG-8 trial treated with adjuvant endocrine therapy alone[J]. Ann Oncol, 2014,25(2):339 – 345.

[59] Turner BM, Gimenez-Sanders MA, Soukiazian A, et al. Risk stratification of ER-positive breast cancer patients: a multi-institutional validation and outcome study of the Rochester Modified Magee algorithm(RoMMa) and prediction of an Oncotype DX® recurrence score <26[J]. Cancer Med, 2019,8(9):4176 – 4188.

[60] Genomic Health Annual Report 2017[EB/OL]. Available from: https://www. annualreports. com/HostedData/AnnualReportArchive/g/NASDAQ_GHDX_2017. pdf.

[61] Duffy MJ, O'Donovan N, McDermott E, et al. Validated biomarkers: the key to precision treatment in patients with breast cancer[J]. Breast, 2016,29:192 – 201.

[62] Jacobs VR, Augustin D, Wischnik A, et al. Concordance rates of biomarkers uPA and PAI-1 results in primary breast cancer vs. consecutive tumor board decision and therapy performed in clinical hospital routine: results of a prospective multi-center study at certified breast centers[J]. Breast, 2016,29:208 – 212.

[63] Tang P, Skinner KA, Hicks DG. Molecular classification of breast carcinomas by immunohistochemical analysis: are we ready? [J]. Diagn Mol Pathol, 2009,18(3):125 – 132.

[64] Turner BM, Hicks DG. Pathologic diagnosis of breast cancer patients: evolution of the traditional clinical-pathologic paradigm toward "precision" cancer therapy[J]. Biotech Histochem, 2017,92(3):175 – 200.

[65] Subik K, Lee JF, Baxter L, et al. The expression patterns of ER, PR, HER2, CK5/6, EGFR, Ki-67 and AR by immunohistochemical analysis in breast cancer cell lines[J]. Breast Cancer(Auckl), 2010,4:35 – 41.

[66] Voduc KD, Cheang MC, Tyldesley S, et al. Breast cancer subtypes and the risk of local and regional relapse[J]. J Clin Oncol, 2010, 28(10):1684 – 1691.

[67] Goldstein NS, Hewitt SM, Taylor CR, et al. Recommendations for improved standardization of immunohistochemistry[J]. Appl Immunohistochem Mol Morphol, 2007,15(2):124 – 133.

[68] Brunelli M, Manfrin E, Martignoni G, et al. HER-2/neu assessment in breast cancer using the original FDA and new ASCO/CAP guideline recommendations: impact on selecting patients for herceptin therapy [J]. Am J Clin Pathol, 2008,129(6):907 – 911.

[69] Middleton LP, Price KM, Puig P, et al. Implementation of American Society of Clinical Oncology/College of American Pathologists HER2 Guideline Recommendations in a tertiary care facility increases HER2 immunohistochemistry and fluorescence in situ hybridization concordance and decreases the number of inconclusive cases[J]. Arch Pathol Lab Med, 2009,133(5):775 – 780.

[70] Cohen DA, Dabbs DJ, Cooper KL, et al. Interobserver agreement among pathologists for semiquantitative hormone receptor scoring in breast carcinoma[J]. Am J Clin Pathol, 2012,138(6):796 – 802.

[71] Vergara-Lluri ME, Moatamed NA, Hong E, et al. High concordance between HercepTest immunohistochemistry and ERBB2 fluorescence in situ hybridization before and after implementation of American Society of Clinical Oncology/College of American Pathology 2007 guidelines [J]. Mod Pathol, 2012,25(10):1326 – 1332.

[72] Yildiz-Aktas IZ, Dabbs DJ, Cooper KL, et al. The effect of 96-hour formalin fixation on the immunohistochemical evaluation of estrogen receptor, progesterone receptor, and HER2 expression in invasive breast carcinoma[J]. Am J Clin Pathol, 2012,137(5):691 – 698.

[73] Bartlett JM, Thomas J, Ross DT, et al. Mammostrat as a tool to stratify breast cancer patients at risk of recurrence during endocrine therapy [J]. Breast Cancer Res, 2010,12(4):R47.

[74] Ring BZ, Seitz RS, Beck R, et al. Novel prognostic immunohistochemical biomarker panel for estrogen receptor-positive breast cancer [J]. J Clin Oncol, 2006,24(19):3039 – 3047.

[75] Ross DT, Kim CY, Tang G, et al. Chemosensitivity and stratification by a five monoclonal antibody immunohistochemistry test in the NSABP B14 and B20 trials[J]. Clin Cancer Res, 2008,14(20): 6602 – 6609.

[76] Bartlett JM, Bloom KJ, Piper T, et al. Mammostrat as an immuno-

histochemical multigene assay for prediction of early relapse risk in the tamoxifen versus exemestane adjuvant multicenter trial pathology study[J]. J Clin Oncol, 2012,30(36):4477 – 4484.

[77] Acs G, Kiluk J, Loftus L, et al. Comparison of Oncotype DX and Mammostrat risk estimations and correlations with histologic tumor features in low-grade, estrogen receptor-positive invasive breast carcinomas[J]. Mod Pathol, 2013,26(11):1451 – 1460.

[78] Stephen J, Murray G, Cameron DA, et al. Time dependence of biomarkers: non-proportional effects of immunohistochemical panels predicting relapse risk in early breast cancer[J]. Br J Cancer, 2014, 111(12):2242 – 2247.

[79] Mislick K, Schonfeld W, Bodnar C, et al. Cost-effectiveness analysis of Mammostrat® compared with Oncotype DX® to inform the treatment of breast cancer[J]. Clinicoecon Outcomes Res, 2014,6:37 – 47.

[80] Cuzick J, Dowsett M, Pineda S, et al. Prognostic value of a combined estrogen receptor, progesterone receptor, Ki-67, and human epidermal growth factor receptor 2 immunohistochemical score and comparison with the Genomic Health recurrence score in early breast cancer[J]. J Clin Oncol, 2011,29(32):4273 – 4278.

[81] Dowsett M, Allred C, Knox J, et al. Relationship between quantitative estrogen and progesterone receptor expression and human epidermal growth factor receptor 2(HER-2) status with recurrence in the Arimidex, Tamoxifen, Alone or in Combination trial[J]. J Clin Oncol, 2008,26(7):1059 – 1065.

[82] Bartlett JM, Christiansen J, Gustavson M, et al. Validation of the IHC4 breast cancer prognostic algorithm using multiple approaches on the multinational TEAM clinical trial[J]. Arch Pathol Lab Med, 2016,140(1):66 – 74.

[83] Elsamany S, Elmorsy S, Alzahrani A, et al. Predictive value of IHC4 score for pathological response to neoadjuvant chemotherapy in hormone receptor-positive breast cancer[J]. Asian Pac J Cancer Prev, 2015,16(17):7975 – 7979.

[84] Sheri A, Smith IE, Hills M, et al. Relationship between IHC4 score and response to neo-adjuvant chemotherapy in estrogen receptor-positive breast cancer[J]. Breast Cancer Res Treat, 2017,164(2):395 – 400.

[85] Barton S, Zabaglo L, A'Hern R, et al. Assessment of the contribution of the IHC4+ C score to decision making in clinical practice in early breast cancer[J]. Br J Cancer, 2012,106(11):1760 – 1765.

[86] Lakhanpal R, Sestak I, Shadbolt B, et al. IHC4 score plus clinical treatment score predicts locoregional recurrence in early breast cancer [J]. Breast, 2016,29:147 – 152.

[87] Flanagan MB, Dabbs DJ, Brufsky AM, et al. Histopathologic variables predict Oncotype DX recurrence score[J]. Mod Pathol, 2008, 21(10):1255 – 1261.

[88] Tang P, Wang J, Hicks DG, et al. A lower Allred score for progesterone receptor is strongly associated with a higher recurrence score of 21-gene assay in breast cancer[J]. Cancer Invest, 2010,28(9): 978 – 982.

[89] Allison KH, Kandalaft PL, Sitlani CM, et al. Routine pathologic parameters can predict Oncotype DX recurrence scores in subsets of ER positive patients: who does not always need testing? [J]. Breast Cancer Res Treat, 2012,131(2):413 – 424.

[90] Klein ME, Dabbs DJ, Shuai Y, et al. Prediction of the Oncotype DX recurrence score: use of pathology-generated equations derived by linear regression analysis[J]. Mod Pathol, 2013,26(5):658 – 664.

[91] Turner BM, Skinner KA, Tang P, et al. Use of modified Magee equations and histologic criteria to predict the Oncotype DX recurrence score[J]. Mod Pathol, 2015,28(7):921 – 931.

[92] Kim HS, Umbricht CB, Illei PB, et al. Optimizing the use of gene expression profiling in early-stage breast cancer[J]. J Clin Oncol, 2016,34(36):4390 – 4397.

[93] Bhargava R, Clark BZ, Dabbs DJ. Breast cancers with Magee equation score of less than 18, or 18-25 and mitosis score of 1, do not require Oncotype DX testing: a value study[J]. Am J Clin Pathol, 2019,151(3):316 – 323.

[94] Bhargava R, Clark BZ, Carter GJ, et al. The healthcare value of the Magee Decision Algorithm™: use of Magee Equations™ and mitosis score to safely forgo molecular testing in breast cancer[J]. Mod Pathol, 2020,33(8):1563 – 1570.

[95] Harowicz MR, Robinson TJ, Dinan MA, et al. Algorithms for prediction of the Oncotype DX recurrence score using clinicopathologic data: a review and comparison using an independent dataset[J]. Breast Cancer Res Treat, 2017,162(1):1 – 10.

[96] Hou Y, Tozbikian G, Zynger DL, et al. Using the modified Magee equation to identify patients unlikely to benefit from the 21-gene recurrence score assay(Oncotype DX assay)[J]. Am J Clin Pathol, 2017, 147(6):541 – 548.

[97] Hou Y, Zynger DL, Li X, et al. Comparison of Oncotype DX with modified Magee equation recurrence scores in low-grade invasive carcinoma of breast[J]. Am J Clin Pathol, 2017,148(2):167 – 172.

[98] Sughayer M, Alaaraj R, Alsughayer A. Applying new Magee equations for predicting the Oncotype Dx recurrence score[J]. Breast Cancer, 2018,25(5):597 – 604.

[99] Robertson SJ, Pond GR, Hilton J, et al. Selecting patients for Oncotype DX testing using standard clinicopathologic information[J]. Clin Breast Cancer, 2020,20(1):61 – 67.

[100] Farrugia DJ, Landmann A, Zhu L, et al. Magee equation 3 predicts pathologic response to neoadjuvant systemic chemotherapy in estrogen receptor positive, HER2 negative/equivocal breast tumors [J]. Mod Pathol, 2017,30(8):1078 – 1085.

[101] Bhargava R, Esposito NN, O Connor SM, et al. Magee equations™ and response to neoadjuvant chemotherapy in ER+/HER2-negative breast cancer: a multi-institutional study[J]. Mod Pathol, 2021, 34(1):77 – 84.

[102] Hou Y, Moosavi HS, Wei L, et al. Magee equation recurrence score is associated with distal metastatic risk in male breast carcinomas: experience from two institutions[J]. Am J Clin Pathol, 2018,150(6):491 – 498.

乳腺癌预后和预测标志物的演变

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Hani Katerji，医学博士，于叙利亚阿勒颇大学获得医学学位。在罗切斯特大学医学中心解剖和临床病理学科完成了住院医师培训，接着继续完成了一年的血液病理学和分子病理学研究领域的训练。随后，在罗切斯特大学又完成了血液病理、妇科和乳腺病理领域的专科培训。Katerji 博士获得解剖病理学和临床病理学专业认证，目前是罗切斯特大学病理和检验医学系的助理教授。他的研究兴趣包括基因组分析检验在乳腺癌中作用的研究。

［**摘要**］　乳腺癌是世界欠发达地区妇女最常见的癌症死因，也是世界较发达地区妇女癌症死亡的第二大原因。乳腺癌治疗方案不断发展，现有多种治疗方式可供选择。然而，寻找可靠的预测和预后的生物标志物来帮助那些最有可能对特定疗法有效的乳腺癌患者选择合适的治疗方法仍然是一项重大挑战，并且这在过去的几十年里一直是许多课题组的研究焦点。在该篇综述中，我们试图对当前乳腺癌预后和预测标志物进行回顾，包括传统的、免疫组化的和基因组的分析，并评估这些标志物的潜在临床应用。

［**关键词**］　乳腺癌；　预后；　预测；　生物标志物；　演变

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