Review Article

Breast cancer gene expression signatures: development and clinical significance—a narrative review

Siyan Li, Xinmiao Yu, Yingying Xu

Department of Breast Surgery, The First Hospital of China Medical University, Shenyang, China

Contributions: (I) Conception and design: All authors; (II) Administrative support: X Yu, Y Xu; (III) Provision of study materials or patients: X Yu, Y Xu; (IV) Collection and assembly of data: S Li, X Yu; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yingying Xu. Department of Breast Surgery, The First Hospital of China Medical University, Shenyang, China. Email: xuyingying@cmu.edu.cn.

Background and Objective: Breast cancer gene expression signatures are developing rapidly and are expected to better understand the intrinsic features of the tumor, and also to optimize the treatment strategy in clinical practice. This review is to summarize the controversy and consensus in clinical practice of gene expression signatures, and to provide our perspective on these issues as well as recommendation for future direction.

Methods: We reviewed English publications in PubMed related to breast cancer gene expression signatures from 2002 to 2022.

Key Content and Findings: Five mature commercial gene expression signatures: Oncotype, MammaPrint, Prosigna/PAM50, EndoPredict and Breast Cancer Index (BCI) are available to provide the prognostic and predictive assessment. Although they could help to evaluate the risk of recurrence and to predict the benefits of certain treatments, their applications remain challenging. Treatment decisions should be determined by a combination of related clinical pathological factors in clinical practice.

Conclusions: Gene expression signatures could assist in the determination of the adjuvant therapy of early-stage breast cancer. The prospective randomized clinical trials showed that chemotherapy may be exempted in low-risk patients. More sufficient data are expected for the application in radiotherapy, extended endocrine therapy, and neoadjuvant treatment. The treatment cannot be determined by a single factor but by comprehensive assessments of clinicopathological factors, test purpose, and cost-effectiveness. Patients will benefit from personalized treatments with the publication of further evidence.

Keywords: Breast cancer; gene expression signature; prognosis; prediction

Received: 31 July 2022; Accepted: 18 October 2022; Published online: 27 October 2022.

doi: 10.21037/tbcr-22-39

View this article at: https://dx.doi.org/10.21037/tbcr-22-39

Introduction

With the development of breast cancer biology, the diagnosis and treatment process has transited from clinicopathology-based to personalized decision-making. The four critical biomarkers to classify breast cancer molecular subtypes are estrogen receptor (ER), progesterone receptor (PR), HER2 and Ki67 by immunohistochemistry (1,2). The intrinsic mechanism and assays of gene expression signatures could guide clinical treatment and facilitate the understanding of breast cancer, as well as the risk assessment of recurrence (3). With reference to these signatures, the optimization of strategy is available to avoid over-or under-treatment. This benefits the patients while reducing the treatment-related adverse effect. "Adjuvant online", an early model for the assessment of prognosis and recurrence risk, is limited mainly to ER-positive, HER2-negative breast cancer by classifying the tumors as clinical high- or low-risk based on histological

Table 1 The search strategy summary

Items	Specification
Date of search	June 1, 2022 to July 1, 2022
Databases and other sources searched	PubMed
Search terms used	Gene expression, genetic test, breast cancer, prognosis, prospective study
Timeframe	2002–2022
Inclusion and exclusion criteria	Inclusion: (I) articles in English; (II) article types were research articles and reviews
Selection process	The included literature was selected by author SL and author XY, reviewed by author YX

grade, lymph node (LN) status and tumor size (4). It is expected to adopt more personalized prognostic and predictive signatures to present the characteristics of the disease by exploring the internal features of the tumor (5). With the retrospective analysis of prospective clinical trials, a certain signature or panel was established independent of other prognostic factors or treatment, to assess the risk of local or distant recurrence (DR) (6); and the patients with breast cancer were assigned to different groups based on the recurrence score (RS) to predict the prognosis or the efficacy of a certain therapy (7); the predictions were then verified in various cohorts or study populations, and eventually, the efficacy was validated in prospective clinical trials (8). These procedures are already completed by the manufacturers of commercialized gene expression signature assays, yet unresolved problems and controversies are still observed in clinical application. The objective of this review is to summarize the controversy and consensus on gene assays in clinical practice by arranging related evidence-based medical evidence. The novelty of this review is based on the practical questions from the prognostic and therapy-predictive application of breast cancer gene expression assays and provide our perspective on these issues as well as recommendation for future direction according to domestic clinical practice. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tbcr.amegroups.com/article/view/10.21037/tbcr-22-39/rc).

Methods

This narrative literature review was created by searching PubMed. The search terms we used include gene expression, genetic test and so on. The literature search time span was from June 2022 to July 2022. The language was restricted to English. For further information, please see *Table 1*.

Application of prognosis signature of breast cancer

Which gene expression signature can be used for prognostic assessment?

Five commercialized gene signature assays are currently available, and their applications are summarized in *Table 2*. The Oncotype DX (21-gene) was developed from the NSABP-B14 study and is applicable to hormone receptor (HR)-positive, HER2-negative ($HR^+/HER2^-$), and LN-negative (LN–) early-stage breast cancer. The RS is calculated based on the expression of 21 genes and classified as low- (<18), intermediate- (18 to 30), and high- (≥31) risk initially. The 10-year recurrence risk is 6.8%, 14.3%, and 30.5%, respectively, and the study showed that RS score is superior to age and tumor size in predictive power (6). This stratified prediction was later verified in various studies worldwide, such as NSABPB20 (7,9,10). In the following 21-gene-related studies, the stratification of the RS score was changed and the stratification generally accepted is low- (0 to 10), intermediate- (11 to 25), and high- (26 to 100) risk groups, whereas in the low-risk group, the 5-year survival of the patients with endocrine therapy alone was 98% and the recurrence-free survival (RFS) was 99.3% (8). MammaPrint (70-gene) is developed based on the clinical outcome of patients and a gene panel is selected indifferently. The patients are classified as high risk and low risk. The 5-year distant metastatic free survival (DMFS) was 94.4% in patients of the low-risk group without chemotherapy and

Table 2 Main characters of five commercial gene expression signatures

Signatures	Gene	Applicability	Stratification factors	Risk groups
Oncotype	21 ($HR^+/HER2^-$)	LN–/LN+ (pre/post-menopausal)	Recurrence score	Low/mid/high-risk group
MammaPrint	70 ($HR^+/HER2^-$)	LN–/LN+ (pre/post-menopausal)	–	Good/poor prognosis
Prosigna/PAM50	50 ($HR^+/HER2^-$)	LN–/LN+ (post-menopausal)	Risk of recurrence	Low/mid/high-risk group
EndoPredict	12 ($HR^+/HER2^-$)	LN–/LN+ (post-menopausal)	Risk score	Low/high-risk group
BCI	11 ($HR^+/HER2^-$)	LN–/LN+ (post-menopausal)	H/I ratio	Low/high-risk group

HER2, human epidermal growth factor receptor 2; BCI, Breast Cancer Index; LN, lymph node; HR, hormone receptor; H/I ratio, HOXB13/IL17BR.

the prognostic value was further validated in other studies too (11-13). Prosigna/PAM50 (50-gene) could predict the 10-year DR of $HR^+/HER2^-$ breast cancer. The 10-year DR of the low- and high-risk LN– group was 2% and 11.5%, respectively (14). EndoPredict (EP) (12-gene) and Endoclinic (combine with the anatomic factors) focus on the 10-year distant recurrence, which was 8% and 22% in the low- and high-risk groups, respectively (15). In summary, the common gene assays all presented reliable prognostic values and suggested a good prognosis in patients in the low-risk group with endocrine therapy alone in $HR^+/HER2^-$ breast cancer. However, the prognosis assessment is only considered a supplementary diagnosis when traditional clinicopathological factors are not assessable.

Are there any ethnic differences in the prognostic assessment of gene expression signatures?

From the aspect of gene level, the prognosis varies in different human races, and the prognosis of various subtypes differs in ethnic groups (16). This is specifically observed between Western populations and Asians. The number of Asian patients enrolled in the gene assays trials was limited despite their presence. For instance, in the TAILORx study, only 135 Asian patients (135/10,046) were involved (8). In addition, the analysis based on the Surveillance, Epidemiology, and End Results (SEER) database showed that the prognosis of patients in different risk groups of the Oncotype (21-gene) varied significantly among races (17). Though multiple factors contribute to the outcome of the disease, the above results suggested that race may be a variable in the gene assay models. Therefore, it is urgent to acquire an assessment of Asian population data. The RecurIndex (RI) score of the 28-gene assay predicts the risk of local recurrence and distant metastasis based on the gene expression and clinicopathological factors (age, number of metastatic LNs, lympho-vascular invasion (LVI), ER status, tumor size, and grades) (18). Internal and external validations were also performed in different cohorts (19-21). The published results proved the prognostic value of the 28-gene assay, and hopefully, more validations will be carried out and eventually applied to clinical practice for Asian population.

How to understand and apply the inconsistent results?

For clinical trials of new treatments or medicine, direct head-to-head comparative studies are rare, and it is challenging to draw clear conclusions. Similarly, it is also difficult to decide whether different predictive gene assays are comparable, and which has a better prognostic efficiency or is more accurate in predicting outcomes (22). The risk assessment ability of gene assay is independent of other traditional factors (23). Compared with the conventional risk assessment for clinical factors, the results of gene expression signatures may be opposite to those in clinical low-risk or high-risk groups (24). In another case, different genetic assessments applied to the same sample may also result in the inconsistency of the risk group (25). Several articles have compared some gene assays but with the limitations of sample size and discordant risk stratification (25-27). A recently published article from the TransATAC study has discussed the molecular feature of gene assays that lead to the differences. According to the four modules of Oncotype RS system, RS is determined more strongly by the estrogen-related features, whereas PAM50 risk of recurrence (ROR), EP, and Breast Cancer Index (BCI) are proliferation features dominated (23). This indicates that although the five above commonly used assays are approved for marketing, clinical assessment is still the basis for personalized treatment and genetic assessments are for assistant diagnosis only. The 21- and 70-gene assays are the gene expression signatures with the most available evidence, yet the assays required should be selected according to the assessment purposes.

Can gene expression signatures identify the risk beyond 5 years?

The 21-gene assay was validated in the TransATAC, NSABP B-20, and B-14 studies for the prognosis value of 5 to 10 years after diagnosis (6,7,9). The 70-gene assay was also studied in the MINDACT trial for long-term prognosis and the updated follow-up results reported showed that the 8-year of distant metastasis-free interval (DMFI) and breast cancer-specific survival (BCSS) in the ultra-low-risk group was up to 97% and 99.6% respectively (24,28). Prosigna/PAM50 was also analyzed for late recurrence in HR-positive breast cancer from ATAC and ABCSG8 studies (14,29). EP and EPClin (combination with clinicopathological factors) were particularly focused on the risk assessment of 0–5-year and 5–10-year recurrence in patients who had completed 5-year endocrine therapy and the results were verified in different studies cohorts, such as the GEICAM9906 study (30). For prediction of late DR in patients with HR-positive breast cancer, BCI was more predictive than 21-gene and Immunohistochemical 4 (IHC4) (31). These gene tools could help to identify patients who might benefit from extended endocrine therapy.

Are the gene expression signatures applicable to DCIS?

The current prognosis method for ductal carcinoma *in situ* (DCIS) is the Van Nuys prognosis index (VNPI), a scoring system based on tumor size, surgery margin, histology grade, and age (32). Oncotype DX DCIS provided a score from 0 to 100 by using a 12-gene expression analysis (from the Oncotype DX 21-gene subset), which is subdivided into low- (<39), intermediate- (39 to 54), and high- (>55) risk groups in predict 10-year risks. Compared to the low-risk group, patients with a high-risk DCIS RS were exposed to a higher local recurrence rate (DCIS or invasive breast cancer) and gained a more significant absolute benefit from the treatment, such as radiotherapy (33,34). This gene expression signature has been verified in ECOG-ACRIN E5194 Study (35). However, there is no prospective clinical evidence and no recommendations for decision-making guidance.

Application of predictive signature of breast cancer

The critical purpose of gene expression signature is to guide clinical treatment and avoid under-treatment or over-treatment. Different from prognostic assessment, the prediction of the efficacy of therapy is usually addressed in prospective clinical studies. However, such data are limited. The main characteristics of three prospective phase 3 randomized controlled trials are summarized in *Table 3*.

Can gene expression signatures predict the benefits of extended endocrine therapy?

Extended endocrine therapy improves survival in patients with HR-positive breast cancer, but it is still unclear which populations could benefit from the extended treatment. Thus, predictive assays are in urgent demand. As mentioned previously, several multi-gene assays are available in predicting the long-term risk of recurrence. BCI is assessed by the H/I ratio (two-gene expression ratio: HOXB13/IL17BR) of the estrogen signaling pathway and molecular grading index (36). BCI could predict the benefits of extended endocrine therapy in the MA.17 study: a high H/I ratio was statistically significantly associated with a decrease in late recurrence in patients receiving extended letrozole therapy [odds ratio (OR) =0.35; 95% confidence interval (CI): 0.16–0.75; P=0.007]; The interaction between H/I and letrozole treatment was statistically significant (P=0.03) (37). In a retrospective analysis of the aTTom trial, the risk of recurrence-free interval (RFI) was reduced by 65% [hazard ratio: 0.35; 95% CI: 0.15–0.86] and 10.2% absolute reduction (P=0.027) in BCI high-risk patients after extended treatment while BCI low-risk patients did not benefit (38). Meanwhile, BCI was validated in IDEAL trial that it could significantly predict the benefit of letrozole extended treatment (39). In clinical practice, the results of BCI prediction influence the decision on extended endocrine therapy. The prospective clinical study, RESCUE (NCT03503799), is already in progress and aims to meet this urgent clinical need and determine its predictive role in extended endocrine therapy.

Are gene expression signatures applicable to LN-positive breast cancer?

Although the enrolled patients of NSABP B-14 and B-20 (the original studies of the 21-gene assay) were all LN-negative (6,7), the TransATAC retrospective analysis showed that the predictive effect of 21-gene RS was independent of LN status (10). In the RxPONDER study, the 21-gene assay was expected to predict the benefits of adjuvant chemotherapy of $HR^+/HER2^-$ breast cancer

Table 3 Main characters of three phase III randomized controlled trials

Variables	TAILOR-X	MINDACT	Rx-PONDER
No. patients	9,719	6,693	5,051
Gene expression assay	Oncotype (21-gene)	MammaPrint (70-gene)	Oncotype (21-gene)
Eligible patients	$HR^+/HER2^-$	$HR^+/HER2^-$	$HR^+/HER2^-$
	LN–	N0–1 (0–3 N+)	N1 (1–3 N+)
Lymph node status	All LN–	LN–: n=5,288 (79%)	1 N+: n=3,275 (65.3%)
		1–3 N+: n=1,405 (21%)	2–3 N+: n=1,726 (34.4%)
Age or menopausal status	≤50 years: n=3,052 (31.4%)	<50 years: n=2,226 (33.2%)	<50 years: n=1,224 (24.4%)
	Premenopausal: n=3,330 (34%)		Premenopausal: n=1,665 (33.2%)
Primary end point	iDFS	DMFS	iDFS
	ET alone non-inferior to CT + ET in RS 11–25 group	5-year DMFS ≥92% in C-high/G-low without CT	Positive interaction between CT and the continuous RS score
Randomization groups	RS [0–10]: ET (n=1,629, 17%)	C-low/G-low: ET alone (n=2,745, 41%)	RS [0–25]: randomized to ET alone *vs.* CT + ET
	RS [11–25]: randomized to ET alone *vs.* CT + ET (n=6,711, 69%)	C-high/G-low (n=1,550, 23%) & C-low/G-high (n=592, 9%): randomized to ET alone *vs.* CT + ET	
	RS [≥26]: CT (n=1,389, 14%)	C-high/G-high: CT + ET	
Result	iDFS hazard ratio 1.08 (95% CI: 0.94–1.24), P=0.26	5-year DMFS 94.7% (95% CI: 92.5–96.2%)	Interaction between CT and RS, hazard ratio 1.02 (95% CI: 0.98–1.05), P=0.35

CT, chemotherapy; ET, endocrine therapy; C/G, clinical/genomic-risk; LN, lymph node; iDFS, invasive disease-free survival; DMFS, distant metastatic free survival; RS, recurrence score; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; CI, confidence interval.

patients (RS 0–25) with one to three positive axillary LNs. The objective of this prospective trial was to determine the effect of chemotherapy on invasive disease-free survival (iDFS) and DRFS and whether the effect was influenced by RS. The 5-year iDFS was 91% and 92.4% in endocrine therapy alone and combined chemotherapy arm respectively. Unfortunately, the interaction between the treatment and RSs was not significant. Only among premenopausal women, iDFS was improved by chemoendocrine therapy significantly (89% *vs.* 93.9%; hazard ratio: 0.60; 95% CI: 0.43–0.83; P=0.009) (40). The MINDACT study also enrolled patients with one to three positive LNs. At 5 years, the rate of survival without distant metastasis was similar between the endocrine and chemoendocrine treatment arm in the patients who were identified as clinical high-risk and genetic low-risk (94.4% *vs.* 95.9%; hazard ratio: 0.78; 95% CI: 0.50–1.21; P=0.267) (24). Therefore, for breast cancer patients with one to three positive LNs, 70 gene is more sufficiently recommended. LN status is an important factor in risk assessment and one of the key roles in the determination of high risk in clinical assessment. Genetic testing may be considered only when chemotherapy is exempted in LN-positive breast cancer, but personalized assessment is still required.

Are gene expression signatures applicable to premenopausal patients?

For HR-positive breast cancer, the significant effects of gene expression signatures were all confirmed in post-menopausal patients. Pre-menopausal patients were enrolled in three major prospective studies. According to the exploratory analysis of the TAILORx study, patients younger than 50 years of age with a RS of 16–25 may benefit from chemotherapy (8). The subgroup analysis of RxPONDER study also showed significant benefits for premenopausal patients receiving chemotherapy (40). Also, in the MINDACT study, the benefit of $HR^+/HER2^-$ patients who were younger than 50 showed a 5% absolute improvement in distant metastasis-free survival (24). Although this result may be related to chemotherapy-induced amenorrhea,

ovarian suppression is not an alternative to chemotherapy in young pre-menopausal breast cancer patients with genetic intermediate risk according to current knowledge. In clinical practice, the benefits of chemotherapy in premenopausal breast cancer patients should be considered and proceeded comprehensively.

Are gene expression signatures applicable to adjuvant radiotherapy?

Radiotherapy effectively reduces the risk of local recurrence in breast cancer patients but is subject to several adverse effects at the same time, such as radiation pneumonia, heart damage, and skin irritations (41). It has been proved that different molecular subtypes respond differently to radiotherapy (42). Retrospective results of the RI (28-gene) showed that breast cancer patients with positive LNs were predicted in a low-risk group for local recurrence, additional radiotherapy would not benefit significantly (43). Radiation sensitivity signature (RSS), 51 gene signatures related to cell cycle and DNA damage response, is expected to predict the local recurrence risk of breast cancer after breast-conserving surgery and it is not related to the breast cancer subtypes, also it is the most significant factors in predicting the local recurrence of all conventional clinicopathologic features (44). The Adjuvant Radiotherapy Intensification Classifier (ARTIC) (combine 27-gene signature and patient age), developed from the SweBCG91-RT trial, could predict what population of breast cancer patients benefit from radiotherapy after breast-conserving surgery. For patients with low-risk ARTIC scores, the whole breast radiotherapy could improve the 10-year cumulative incidence of local recurrence significantly, but further enhanced benefits of radiotherapy were not predicted in patients with high-risk ARTIC scores (44). Therefore, the current evidence cannot sufficiently support the application of genetic testing to the guidance of adjuvant radiotherapy. Several ongoing studies are exploring the exemption of radiotherapy based on gene expression signatures, including PRESION, IDEA, PRIMETIME, EXPERT, and MA39 TAILOR RT and these results may contribute to the de-escalation of radiotherapy.

Are gene expression signatures applicable to neoadjuvant chemotherapy (NAC) or neoadjuvant endocrine therapy (NET) of HR$^+$/HER2$^-$ breast cancer?

The optimization of the treatment strategy via NAC shows the trends of a precise medicine. But for patients with HR$^+$/HER2$^-$ breast cancer, the benefit of neoadjuvant therapy (NAT) is still unclear. NET is a reasonable option for selective HR$^+$/HER2$^-$ patients due to its stable response rate and lower toxicity, despite the lack of generally recognized strategies (45). From the aspect of response prediction, preoperative endocrine prognostic index (PEPI) score and Ki67 change in the opportunity therapy window facilitates the prediction efficacy of NET (46,47); it is shown in retrospective studies that the Oncotype RS is related to NAT response: the higher RS, the higher pathologic complete response (pCR) rates, whereas the lower RS, the poorer response in HR$^+$/HER2$^-$ breast cancer (48). A recently published prospective study, WSG-ADAPT HR$^+$/HER2$^-$, demonstrated that combining 21-gene assay and NET response could guide systemic therapy in early breast cancer (49). The results from the ABCSG-34 trial showed that EP could predict the response of NAC and NET in patients with HR$^+$/HER2$^-$ breast cancer. Those with higher EP score are more likely to respond to NAC, whereas those with low EP score are more sensitive to NET (50). Besides HR$^+$/HER2$^-$ breast cancers, there is insufficient evidence on the multi-gene signature to optimize the NAT of other molecular subtypes. For HR$^+$/HER2$^-$ breast cancer, the gene expression signatures could help to predict the efficacy of NAC and NET, but only Oncotype and EP have relatively abundant evidence.

Clinical application of gene expression signature in China

Accessibility

The accessibility to gene expression signatures is an issue requiring urgent solutions. Only MammaPrint (70-gene) was approved in China with the authorization of the original company. The widely used 21-gene assay is only the RS calculated with the same algorithm but is not the original product of Oncotype DX, so certain issues are observed during clinical application due to the insufficient techniques and the lack of consistent evaluation of the manufacturers. Therefore, in clinical practice, the companies responsible for the assay must be qualified for the testing based on the testing purposes, and the reports should be interpreted carefully and comprehensively. Different from that in China, the medical treatment cost is huge in Western countries even though most costs are covered by insurance. Despite this, the chemotherapy exemption by genetic

testing is still cost-effective (51). Yet, relevant studies are few in China and cannot confirm the cost-effectiveness of gene expression signatures for the time being.

How to balance the gene expression signatures and traditional clinicopathological factors?

In China, traditional clinicopathological factors remain the basis of breast cancer treatment and prognostic assessment in clinical practice, despite some results indicating that the gene expression-based risk assessment is independent of conventional prognostic factors. The clinical guidelines in China stated that the risk assessment and therapy decisions are still based on clinical factors, such as the number of positive LN, tumor size, age, LVI, HR status, HER2 status, and Ki67. 21-gene and 70-gene assays are only considered for intermediate-risk $HR^+/HER2^-$ patients with a strong willingness for chemotherapy exemption.

Guideline recommendations

Based on the available data, the clinical guidelines provide recommendations for the selection of gene expression signatures, including 21-gene (Oncotype DX), 70-gene (MammaPrint), 50-gene (PAM50), 12-gene (EP), and BCI assays. Unlike traditional breast cancer biomarkers (ER/PR/HER2/Ki67), recommendations of clinical applications vary from the different expert panels because of the additional update time, criteria of literature review, and level of evidence system. The use of the 21-gene assay is preferred by the National Comprehensive Cancer Network (NCCN) breast cancer panel for prognosis and prediction of chemotherapy benefits. Other gene expression assays can provide prognostic information, but the predictive value of chemotherapy benefit is unknown. The American Society of Clinical Oncology (ASCO) also provides recommendations for adjuvant therapy decision-making based on the Oncotype Dx RS and age of patients in HR^+/HER^- early-stage breast cancer. The MammaPrint guides the decisions on withholding adjuvant chemotherapy in patients with HR^+ LN-negative and selective patients with LN-positive breast cancer or at high clinical risk. In contrast, the St. Gallen Conesus penal discussed disease management in specific situations. Most of the panel favored the consideration of genomic signatures in most of the clinical situation when chemotherapy is considered in $ER^+/HER2^-$ early-stage breast cancer with negative LN or limited positive (1 to 3) LN on the basis of mature evidence from prospective trials. Tumor grade and premenopausal should be taken into consideration too. But for pN2 or higher stage, chemotherapy is recommended as standard treatment (52). The European Society of Medical Oncology (ESMO) Guideline Committee produced evidence-based recommendations for gene expression assays, not particular for the LN status and ages, but for the uncertainty of adjuvant chemotherapy considering clinicopathological factors to guide the decision-making of systemic treatment. MammaPrint, Oncotype DX, EP, Prosigna PAM50, and BCI are also applicable.

In China, the Chinese Anti-Cancer Association, Committee of Breast Cancer Society (CACA-CBCS) guideline (version 2021) only recommends 21-gene and 70-gene assays, and the application of BCI, EP, or PAM50 is optional. For the decision-making of adjuvant chemotherapy, the risk assessment of recurrence and metastasis of breast cancer is based on clinicopathological factors. In the intermediate-risk group, the gene expression signatures should be used only when the exemption from chemotherapy is considered. Chinese Society of Clinical Oncology (CSCO) breast cancer diagnosis and treatment guidelines (version 2022) announced that MammPrint has been approved in China and it is recommended for breast cancer patients requiring multi-gene expression profiling. In addition, CSCO guidelines noted that a reference basis for adjuvant chemotherapy and radiotherapy is provided by the 28-gene signature (RI) for Asian patients with ER-, PR-positive, and HER2-negative early-stage breast cancer (53).

Future direction

Gene expression signatures are mainly used for prognostic assessment and therapy efficacy prediction in clinical practice for the guidance of clinical strategy. The following should be taken into account for future studies: (I) to further validate the efficacy of gene expression signatures in the prediction of long-term recurrence risk, especially for 5–10 years; (II) to develop gene expression signatures specifically for the Chinese population with relevant validations to guide future treatments; (III) to evaluate the cost-effectiveness of gene assays; (IV) to explore and establish the prediction model for de-escalation of local treatment, and (V) to study the characteristics of the population who can benefit from NAT.

Conclusions

Gene expression signatures assist in the determination

of the adjuvant therapy of early-stage breast cancer. The MINDACT and TAILORx trial, phase III prospective randomized clinical trials, showed that chemotherapy may be exempted in low-risk patients. For post-menopausal patients with $HR^+/HER2^-$ breast cancer, the application of such assays should be comprehensibly considered. More sufficient data are expected for the application in radiotherapy, extended endocrine therapy, and neoadjuvant treatment. The treatment cannot be determined by a single factor but by comprehensive assessments of clinicopathological factors, test purpose, and cost-effectiveness. Patients will benefit from personalized treatments with the publication of further studies.

Acknowledgments

Funding: This work was supported by the Shenyang Bureau of Science and Technology (No. RC190393), Shanghai Cancer Prevention and Anti-Cancer development Foundation (No. CYBER-2021-A02) and Wu Jieping Medical Foundation (No. 320.6750.2021-10-108).

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist (available at https://tbcr.amegroups.com/article/view/10.21037/tbcr-22-39/rc).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tbcr.amegroups.com/article/view/10.21037/tbcr-22-39/coif). YX serves as an unpaid editorial board member of *Translational Breast Cancer Research* from May 2021 to April 2023. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/tbcr-22-39
Cite this article as: Li S, Yu X, Xu Y. Breast cancer gene expression signatures: development and clinical significance—a narrative review. Transl Breast Cancer Res 2023;4:7.

