Gene Expression Assays to Tailor Adjuvant Endocrine Therapy for HR+/HER2− Breast Cancer

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ABSTRACT

Adjuvant endocrine therapy (ET) represents the standard of care for almost all hormone receptor (HR)+/HER2− breast cancers, and different agents and durations are currently available. In this context, the tailoring and optimization of adjuvant endocrine treatment by reducing unnecessary toxic treatment while taking into account the biological heterogeneity of HR+/HER2− breast cancer represents a clinical priority. There is therefore a significant need for the integration of biological biomarkers in the choice of adjuvant ET beyond currently used clinicopathological characteristics. Several gene expression assays have been developed to identify patients with HR+/HER2− breast cancer who will not derive benefit from the addition of adjuvant chemotherapy. By enhancing risk stratification and predicting therapeutic response, genomic assays have also shown to be a promising tool for optimizing endocrine treatment decisions. In this study, we review evidence supporting the use of most common commercially available gene expression assays [Oncotype DX, MammaPrint, Breast Cancer Index (BCI), Prosigna, and EndoPredict] in tailoring adjuvant ET. Available data on the use of genomic tests to inform extended adjuvant treatment choice based on the risk of late relapse and on the estimated benefit of a prolonged ET are discussed. Moreover, preliminary evidence regarding the use of genomic assays to inform de-escalation of endocrine treatment, such as shorter durations or omission, for low-risk patients is reviewed. Overall, gene expression assays are emerging as potential tools to further personalize adjuvant treatment for patients with HR+/HER2− breast cancers.

Introduction

Hormone receptor (HR)+/HER2− breast cancer represents the most frequent breast cancer subtype, accounting for more than two thirds of new breast cancer diagnoses (1). Adjuvant endocrine therapy (ET) has been widely recognized as a cornerstone in the clinical management of early-stage HR+/HER2− breast cancers, providing a reduction of almost 40% in the risk of recurrence as well as a long-term reduction in breast cancer–related mortality (2). Indeed, randomized trials have established different ET options with tamoxifen, aromatase inhibitors (AI), and, for high-risk premenopausal patients, ovarian function suppression (OFS), for at least 5 years as standard adjuvant therapy, which is routinely prescribed in almost all newly diagnosed HR+/HER2− breast cancers (3, 4).

However, the optimal regimen and duration of ET for a specific patient is often uncertain, and there is a significant clinical unmet need for biomarkers in guiding this choice. On one hand, early-stage HR+/HER2− breast cancer has been associated with a persistent long-term risk of relapse, and more than half of recurrences occur beyond 5 years from diagnosis (5). In this context, several large randomized trials have proven that extended adjuvant ET beyond 5 years provides a significant, although modest, benefit in reducing the risk of late relapse, and this approach is currently recommended by international guidelines for high-risk patients (3, 4). However, prolonged ET is also associated with higher adverse events (6, 7), highlighting the need of accurately selecting patients who may be more likely to benefit from an extended treatment.

On the other hand, some markedly indolent tumors with an excellent long-term prognosis have been described among HR+/HER2− breast cancers. This opens the possibility of a de-escalation of standard 5-year ET in terms of reduced duration or omission (8). Indeed, significant toxicities and quality-of-life impairment have been reported among patients receiving ET, and the identification of subgroups of patients who may be safely treated with shorter therapies is of critical interest (9). Moreover, in premenopausal patients, the identification of low-risk subgroups could avoid more toxic combinations, such as the addition of OFS to ET and, in the context of OFS, the use of an AI rather than tamoxifen.

HR+/HER2− breast cancer is a biologically heterogeneous disease; therefore, the sensitivity to ET and its clinical benefit are markedly variable. However, current clinical recommendations for ET are mostly based on clinicopathological features, and there is a lack of biological predictive biomarkers to optimize patient selection. In the past two decades, genomic signatures have been developed to identify patients at a relatively low risk of relapse who do not derive benefit from the addition of adjuvant chemotherapy and may be treated with ET alone (10–12). Several assays are currently commercially available and are routinely used in clinical practice, including Oncotype DX, MammaPrint, Breast Cancer Index (BCI), EndoPredict, and Prosigna (based on the PAM50 algorithm). Although originally mainly developed to guide decision on adjuvant chemotherapy in combination with ET, a growing body of evidence has shown that genomic tests might be potentially helpful in tailoring adjuvant ET in early-stage

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HR+/HER2− breast cancer as well. Identifying categories at higher or lower risk of relapse, as well as characterizing endocrine sensitivity, genomic assays may represent a valid tool to guide the management of adjuvant ET toward more or less intensive strategies.

In this work, we review available evidence evaluating the potential use of commercially available gene expression signatures in the management of adjuvant hormonal therapy, both in the context of escalation (i.e., extended ET) and de-escalation strategies.

Escalation Strategies: Extended Adjuvant Treatment

Several multigene assays have been tested to predict the risk of late recurrence and the benefit of extended ET (**Table 1**).

BCI

BCI is a gene expression–based signature consisting of two functional biomarker panels, the molecular grade index (MGI) and the two-gene ratio *HOXB13*/*IL17BR* (H/I), evaluating tumor proliferation and estrogen signaling, respectively. The two components are integrated in the BCI score. BCI has been validated as a prognostic biomarker in untreated and treated early-stage HR+/HER2− breast cancers, predicting disease-free survival and overall survival (OS) (13–16).

BCI has been evaluated in several trials as a prognostic biomarker to predict late recurrence after 5 years of ET, with the aim of identifying patients with a persistent high risk of recurrence who could benefit from extended adjuvant treatment.

Zhang and colleagues (17) first reported the prognostic performance of BCI in predicting the risk of late relapse in two independent cohorts of early-stage breast cancer without nodal involvement (the Stockholm tumor-associated macrophage randomized trial cohort, $n = 317$, and a multi-institutional cohort, $n = 358$). The prognostic ability of BCI in predicting late distant relapse between 5 and 10 years was further confirmed in 1,102 patients with HR+/HER2− breast cancer treated with either 5 years of tamoxifen or anastrozole in the ATAC trial (18).

In order to further improve its ability to predict long-term outcome in HR+ breast cancer with nodal involvement, BCI has been integrated with relevant histopathological features (tumor size and grade) in a model called BCIN+. In a retrospective monocentric analysis from the Massachusetts General Hospital, 349 patients with HR+ breast cancers who remained distant recurrence–free after 5 years were analyzed (23% categorized as BCIN+ low-risk): the risk of distant recurrence in years 5 to 15 was 1.3% (95% CI, 0.0%–3.7%) versus 16.1% (95% CI, 10.6%–21.3%) in the low- and high-risk groups according to BCIN+, respectively. Moreover, BCIN+ remained the most significant prognostic factor after adjustment at multivariate analysis for age, PR status, chemotherapy treatment, ET duration, type of ET, and number of positive lymph nodes (19).

Both BCI and BCIN+ have been further validated in a recent analysis of the TEAM trial in N0 and N1 patients, respectively. In this study, postmenopausal patients with HR+ breast cancer were randomized to exemestane for 5 years or sequential tamoxifen followed by exemestane for a total of 5 years of treatment. Both models were significantly associated with late distant recurrence in patients with both N0 and N1 HR+/HER2− breast cancers ($P = 0.0064$ and $P = 0.0009$, respectively), even after adjustment for age, tumor size, grade, and treatment (20). Similar results were also obtained using BCI and BCIN+ as a continuous risk score (21).

In addition to its prognostic value, the BCI (H/I) ratio has also been shown to predict the likelihood of benefit from extended ET in several randomized trials.

Indeed, a prospective–retrospective case–control analysis of the MA.17 trial, a phase III study randomizing postmenopausal patients with HR+ breast cancers (including a small subgroup of HER2+ breast cancers) treated with 5 years of tamoxifen to additional 5 years of letrozole or placebo, allowed to evaluate the BCI (H/I) ratio in 83 patients with breast cancer recurrence and 166 matched patients without recurrence. Among patients treated with placebo, BCI (H/I)-high was associated with a worse prognosis compared with BCI (H/I)-low ($P = 0.003$; odds ratio = 2.24; 95% CI, 1.09–4.61), consistent with its prognostic role (22). Moreover, extended ET with letrozole was associated with a statistically significant decrease in late recurrence in BCI (H/I)-high patients ($P = 0.007$; odds ratio = 0.35; 95% CI, 0.16–0.75, corresponding to a reduction in the absolute risk of recurrence of 16.5% at 5 years from randomization), whereas no significant reduction in the risk of recurrence with the extended use of letrozole was observed in BCI (H/I)-low patients ($P = 0.35$; ref. 22).

Subsequently, these findings were strengthened by a similar analysis performed in the aTTom trial by Bartlett and colleagues. In this study, 6,956 patients with breast cancer who remained disease-free after at least 4 years of adjuvant tamoxifen treatment were randomized to stop ET or to receive 5 additional years of tamoxifen. Among 2,445 patients with confirmed HR+ status and available BCI results, 789 were node-positive. In this subgroup, only patients classified as BCI (H/I)-high derived a significant benefit from extended tamoxifen treatment in terms of recurrence-free interval (HR = 0.33; 95% CI, 0.14–0.75), whereas no benefit from extended ET was observed in patients classified as BCI (H/L)-low (HR = 1.11; 95% CI, 0.76–1.64; ref. 23, 24).

The predictive value of BCI for extended ET benefit in patients already treated with 5 years of ET which included an AI was evaluated in a prospective–retrospective translational analysis of the IDEAL trial. In this study, 1,824 patients were randomized to receive 2.5 years or 5 years of additional AI treatment after completing the standard adjuvant therapy for 5 years with tamoxifen, an AI, or tamoxifen followed by an AI. A total of 794 patients with breast cancer, who at the time of randomization had already received adjuvant ET including an AI, were analyzed, showing that the use of 5 additional years of letrozole was beneficial in BCI (H/I)-high patients ($P = 0.004$; HR = 0.34; 95% CI, 0.16–0.73), whereas BCI (H/I)-low patients did not derive significant benefit ($P = 0.71$; HR = 0.90; 95% CI, 0.53–1.55; ref. 25).

Finally, the predictive role of BCI for extended ET benefit in patients already treated with 5 years of AI (2,179 patients) was assessed in the NRG Oncology/NSABP B-42 trial. Although no significant association between BCI and extended ET was reported in terms of breast cancer–free interval, in a time-dependent analysis of distant recurrence, BCI (H/I)-high patients showed a statistically significant benefit from extended letrozole treatment after 4 years ($P = 0.003$), whereas BCI (H/I)-low patients did not ($P = 0.28$), consistent with what reported in the previously discussed trials (26).

MammaPrint

MammaPrint is a 70-gene test designed to classify patients into a low-risk and high-risk subgroups based on the risk of recurrence, with the main objective of identifying patients who might safely forgo adjuvant chemotherapy (11). More recently, the development of a more conservative threshold has allowed for the identification,

Table 1. Studies evaluating the risk of late relapse and the benefit of extended ET according to gene expression assays.

Genomic assay	Study	Role	Number of patients	Menopausal status	Lymph nodes status	ET received in the first 5 years	Extended ET	Main findings
BCI	Zhang and colleagues (17)	Prognostic	958	Premenopausal and postmenopausal	N0	Tamoxifen	No	Late (5–10 years) DR-free survival of 97.2%, 92.8%, and 89.9% for BCI low-, intermediate-, and high-risk groups
	Sgroi and colleagues (18)	Prognostic	1,102	Postmenopausal	N0	Tamoxifen or AI	No	Late (5–10 years) DR rates of 3.5%, 13.4%, and 13.3% for BCI low-, intermediate-, and high-risk groups
	Zhang and colleagues (19)	Prognostic	402	Premenopausal and postmenopausal	N+	Tamoxifen or AI	31.3% (not randomized)	Risk of late (5–15 years) DR of 1.3% vs. 16.1% in low- and high-risk BCIN+ groups
	Bartlett and colleagues (20)	Prognostic	3,769	Postmenopausal	N0 and N+	AI ± tamoxifen	No	Late (5–10) DR rates for BCIN+ low- and high-risk groups of 5.4% and 9.3% in the N0 cohort and 5.5% and 12.2% in the N1 cohort
	Sgroi and colleagues (22)	Prognostic and predictive	249	Postmenopausal	N0 and N+	Tamoxifen	Yes (randomized letrozole vs. placebo)	Absolute decrease of 16.5% in late recurrence in BCI (H/I)-high patients treated with extended letrozole therapy
	Noordhoek and colleagues (25)	Predictive	904	Premenopausal and postmenopausal	N0 and N+	Tamoxifen or AI	Yes (randomized letrozole for 2 vs. 5 years)	Significant benefit from extended letrozole-only treatment for BCI (H/I)-high patients (HR = 0.42; 95% CI, 0.21–0.84)
	Bartlett and colleagues (24)	Predictive	789	Premenopausal and postmenopausal	N+	Tamoxifen	Yes (randomized tamoxifen vs. follow-up)	Significant benefit from extended letrozole-only treatment for BCI (H/I)-high patients (HR = 0.33; 95% CI, 0.14–0.75)
	Mamounas and colleagues (26)	Predictive	2,179	Postmenopausal	N0 and N+	AI	Yes (randomized letrozole vs. placebo)	Significant benefit on DR from extended AI therapy in BCI (H/I)-high patients (HR = 0.29; 95% CI, 0.12–0.69)
MammaPrint	Esserman and colleagues (27)	Prognostic	652	Postmenopausal	N0	Tamoxifen	No	Increased long-term breast cancer–specific risk of death in low non–ultralow breast cancers (HR = 4.54; 95% CI, 1.40–14.80) compared with ultralow breast cancers
	Rastogi and colleagues (28)	Predictive	1,866	Postmenopausal	N0 and N+	AI	Yes (randomized letrozole vs. placebo)	DR benefit from extended AI therapy in the low non–ultralow subgroup (HR = 0.42; 95% CI, 0.23–0.76)
	Liefers and colleagues (29)	Predictive	515	Postmenopausal	N0 and N+	Tamoxifen and/or AI	Yes (randomized letrozole for 2 vs. 5 years)	DR benefit from extended AI in the low non–ultralow subgroup (HR = 0.32; 95% CI, 0.12–0.87)
EndoPredict	Dubsky and colleagues (30)	Prognostic	1,702	Postmenopausal	N0 and N+	Tamoxifen ± AI	No	Lower late-DR in the low-risk group compared with the high-risk group ($P = 0.002$)
PAM50	Filipits and colleagues (32)	Prognostic	1,246	Postmenopausal	N0 and N+	Tamoxifen ± AI	No	Late (5–15 year) DR significantly different according to ROR groups (high vs. low: HR = 6.90; 95% CI, 3.08–15.45)
	Sestek and colleagues (33)	Prognostic	2,137	Postmenopausal	N0 and N+	Tamoxifen and/or AI	No	Patients with low-risk ROR presented a 2.4% risk of late (5–10 years) DR compared with 16.6% in the high-risk group

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Table 1. Studies evaluating the risk of late relapse and the benefit of extended ET according to gene expression assays. (Cont'd)

Genomic assay	Study	Role	Number of patients	Menopausal status	Lymph nodes status	ET received in the first 5 years	Extended ET	Main findings
Oncotype DX	Dowsett and colleagues (34)	Prognostic	1,231	Postmenopausal	N0 and N+	Tamoxifen or AI	No	RS did not predict late (5–10 years) DR (HR = 1.28; 95% CI, 0.95–1.72).
	Wolmark and colleagues (35)	Prognostic	1,730	Pre- and postmenopausal	N0 and N+	Tamoxifen	No	Significant association between the RS group and late (5–10 years) DR in the B-28 trial ($P = 0.02$) but not in the B-14 trial ($P = 0.06$)

Abbreviations: CI, confidence interval; DR, distant recurrence; HR, hazard ration.

within the MammaPrint-low group, of a subgroup of patients with extremely favorable outcomes (the ultralow-risk subgroup; ref. 8). Indeed, analyses of ET trials conducted at longer follow-ups, such as a secondary analysis of the Stockholm Tamoxifen (STO-3) trial conducted after a 20-year follow-up period, have reported that patients belonging to the MammaPrint-low breast cancer group, despite an excellent 5-year prognosis, still present a significant risk of late recurrence. The same analysis showed that this risk is mainly driven by the non–ultralow subgroup, which may therefore derive more benefit from extended ET, whereas the ultralow-risk subgroup maintained its favorable outcomes (27).

The utility of the MammaPrint assay in predicting the benefit of extended adjuvant ET was first evaluated in the NRG Oncology/NSABP B-42 trial. In this trial, 1,866 patients already treated with 5 years of an AI and randomized to receive additional 5 years of letrozole or placebo were evaluated by MammaPrint (38% were MammaPrint-high and 62% MammaPrint-low). A significant benefit from extended letrozole, in terms of distant recurrence (HR = 0.43; 95% CI, 0.25–0.74; $P = 0.002$), disease-free survival (HR = 0.67; 95% CI, 0.52–0.85; $P < 0.001$), and breast cancer–free survival (HR = 0.51; 95% CI, 0.35–0.74; $P < 0.001$), was observed in the MammaPrint-low subgroup, specifically in the low but non–ultralow subgroup (HR for distant recurrence 0.42; 95% CI, 0.23–0.76; $P = 0.003$). On the contrary, no significant benefit from extended ET was observed in the MammaPrint-high group for any of the reported outcomes (28).

Recently, a similar analysis was also conducted for patients enrolled in the IDEAL trial (515 patients); consistently with the NRG Oncology/NSABP B-42 trial, the benefit of 5-year extended AI therapy, for both distant recurrence–free survival and recurrence-free interval, was only observed in the MammaPrint low-risk group (HR = 0.42; 95% CI, 0.174–0.996 and HR = 0.43; 95% CI, 0.198–0.934, respectively), mainly driven by the low non–ultralow subgroup, but not in the MammaPrint high-risk group (29).

EndoPredict

EndoPredict is a 12-gene assay developed to predict the likelihood of distant recurrence in HR+/HER2− breast cancers treated with adjuvant ET only.

The prognostic value of EndoPredict for late recurrence was assessed in 1,702 postmenopausal patients treated with 5 years of tamoxifen or tamoxifen followed by an AI in the ABCSG6 and ABCSG8 trials. Patients whose tumors were classified as the EndoPredict low-risk group showed a significantly better clinical outcome compared with the EndoPredict high-risk group in terms of late recurrence ($P = 0.002$), which was maintained at multivariate analysis after adjustment for age, grade, lymph node status, tumor size, and Ki67 (30).

The prospective observational EXET study is currently evaluating the potential impact of EndoPredict in extended ET treatment decision and will also evaluate patients' outcomes. In this study, EndoPredict was performed in patients with HR+/HER2− breast cancers already treated with 5 years of ET, and the impact of the genomic test on clinical decisions regarding extended ET was assessed. Initial results on 411 enrolled patients have recently been reported, showing a strong adherence to EndoPredict results, with all EndoPredict high-risk patients receiving extended therapy (31).

Prosigna® (PAM50)

The PAM50 algorithm has been primarily designed to determine the intrinsic subtype of breast cancers by analyzing the expression

levels of a minimal number of genes (50 genes); in addition, it also provides significant prognostic information in HR+/HER2− breast cancers through the risk of recurrence (ROR) score.

Moreover, PAM50 ROR also showed prognostic ability in identifying patients at higher risk of late recurrence after 5 years of adjuvant ET (years 5–15). In particular, among 1,246 evaluable patients enrolled in the ABCSG-8 trial, the ROR score provided significant prognostic information in addition to clinical factors alone ($P < 0.001$), with patients with low ROR having a 2.4% risk of distant recurrence between years 5 and 15 as compared with 17.5% in patients with high ROR (32). These findings were further confirmed by a combined analysis of the ABCSG-8 and TransATAC trials, which reported a similar trend in a larger cohort of 2,137 postmenopausal patients: patients with low ROR presented a 2.4% risk of late distant recurrence (years 5–10) compared with 16.6% in the high-risk group, and ROR added significant prognostic information to clinical risk factors [as evaluated by the Clinical Treatment Score (CTS)] in the late relapse period (33).

Oncotype DX

Oncotype DX is a 21-gene recurrence score (RS) assay developed and validated to predict chemotherapy benefit in N0 and N+ HR+/HER2− breast cancers.

Regarding the potential prognostic ability of Oncotype DX to predict the risk of late relapse, discordant data have been reported so far. Indeed, the prognostic performance of Oncotype DX in predicting late relapse has been evaluated in the ATAC trial: despite being prognostic for early distant recurrence, as expected, the Oncotype DX RS did not predict late relapse (5–10 years; HR = 1.28; 95% CI, 0.95–1.72; ref. 18, 34).

A similar analysis was also conducted in the NRG Oncology/National Surgical Adjuvant Breast and Bowel Project B-28 and B-14 trials, analyzing 1,065 patients with node-positive HR+ breast cancer treated with chemotherapy plus tamoxifen and 668 patients with node-negative HR+ breast cancers treated with tamoxifen, respectively. In both studies, patients were stratified in three RS groups (<18, 18–30, and >31), with increasing risk groups associated with an increase in distant recurrence risk in years 5 to 10; however, this association reached statistical significance only in the B-28 trial ($P = 0.02$) and not in the B-14 trial ($P = 0.06$; ref. 35).

It should also be pointed out that the previously discussed ATAC trial was also used as a platform to compare the prognostic value of four genomic assays (Oncotype DX, Prosigna, BCI, and EndoPredict) and two clinical/pathological risk scores (the CTS and 4-marker immunohistochemical score). All six scores were significantly associated to distant recurrence between 0 and 10 years among the 774 postmenopausal patients analyzed. However, only Prosigna (HR = 2.77; 95% CI, 1.93–3.96), BCI (HR = 2.30; 95% CI, 1.61–3.30), and EndoPredict (HR = 2.19; 95% CI, 1.62–2.97) provided significant prognostic value for late distant recurrence during years 5 to 10 both in node-positive and node-negative patients. These findings, assessing different genomic assays on the same clinical platform, might in fact suggest the existence of intrinsic differences between the different genomic assays, with BCI, Prosigna, and EndoPredict presenting molecular components in their signatures, which might be more specifically prognostic for late recurrence (36).

Tailoring Adjuvant OFS for Premenopausal Women

Based on the results of the SOFT and TEXT trials, the addition of OFS to adjuvant ET with either tamoxifen or exemestane has been consistently implemented in the adjuvant treatment of high-risk premenopausal HR+ breast cancer patients to reduce the risk of recurrence as compared with adjuvant tamoxifen treatment alone (9). However, the intensification of ET with OFS is also well-known to significantly increase the toxicity of ET in young women, and, therefore, the potential identification of a biomarker to aid decision-making in this setting is particularly appealing.

The prognostic impact of BCI has been evaluated in the SOFT trial, which investigated the addition of OFS to tamoxifen or an AI in premenopausal patients. In particular, BCI was available for 1,687 patients enrolled in the trial and, in this analysis, patients with BCI (H/I)-high status (42%) did not present any benefit by the addition of OFS (HR = 1.03; 95% CI, 0.70–1.53 for exemestane + OFS vs. tamoxifen alone and HR = 1.05; 95% CI, 0.72–1.54 7.3% for tamoxifen + OFS vs. tamoxifen). Paradoxically, a significant benefit was observed for the use of OFS in the BCI (H/I)-low group, with an absolute benefit in terms of 12 years of breast cancer–free interval of 11.6% for exemestane + OFS versus tamoxifen alone (HR = 0.48; 95% CI, 0.33–0.71) and 7.3% for tamoxifen + OFS versus tamoxifen (HR = 0.69; 95% CI, 0.48–0.97) treatment. Consistent results were observed in subgroup analyses stratifying for previous chemotherapy, nodal status, and age. If these results were confirmed, BCI might therefore carry a significant potential as genomic biomarker to predict the benefit of adding OFS to ET in premenopausal patients with breast cancer (37).

Very recently, a similar analysis was also conducted assessing the prognostic impact of PAM50 among 1,066 patients from the SOFT trial. Among the cases analyzed, 64% were classified as low/intermediate ROR and 36% as high ROR; however, the PAM50 ROR score was not predictive of OFS benefit (interaction $P = 0.1$ for exemestane + OFS and $P = 0.2$ for tamoxifen + OFS; ref. 38).

De-escalation: Omission of Endocrine Treatment

MammaPrint

Differently from other genomic assays, MammaPrint was originally developed using data from a cohort of systemically untreated breast cancer patients, showing a 10-year OS of 92% in the low-risk group as compared with 59.5% in the high-risk group (39). Therefore, this 70-gene genomic test represents an ideal tool to evaluate potential de-escalation strategies and has been the most extensively studied assay in this setting (40). In this context, in addition to the original classification in high- and low-risk groups, a lower threshold was developed to allow for further stratification of low-risk patients and to identify a MammaPrint ultralow-risk subgroup with extremely favorable outcomes. This threshold was initially established by Delahaye and colleagues (8) in a cohort of 151 N0 patients, leading to the identification of seven ultralow-risk cases which presented a 20-year breast cancer–specific survival of 100%.

The excellent outcome of ultralow-risk breast cancers treated with standard ET, as compared with low- and high-risk groups, was also reported in an exploratory analysis of the large MINDACT trial. Overall, 1,000 patients (15% of the entire study cohort) were identified as having an ultralow risk of disease. Most of these patients had lymph node–negative tumors (80%) and G1 or G2 tumors (96%); 16% of these patients did not receive any adjuvant treatment. The excellent prognosis of this patient subgroup was confirmed, with an 8-year distant metastasis–free survival of 97.0% and a breast cancer–specific survival of 99.6%, and similar outcomes were

Table 2. Studies evaluating the identification of low-risk breast cancer through genomic tests and its potential use to de-escalate ET strategies.

Study	Test	Number of patients	Menopausal status	Node status	ET	Main findings
Delahaye and colleagues (8)	MammaPrint	453	Premenopausal and postmenopausal	N0	None	20-year breast cancer–specific survival of 100% among ultralow-risk breast cancers
Esserman and colleagues (27)	MammaPrint	652	Postmenopausal	N0	Tamoxifen (2 vs. 5 years) or none	20-year breast cancer survival of 97% for ultralow-risk patients treated with tamoxifen and 94% for ultralow-risk untreated patients
Opdam and colleagues (45)	MammaPrint	135	Postmenopausal	N0	Tamoxifen (1 vs. 3 years) or none	DR-free interval at 10 years of 100% for N0 ultralow-risk breast cancers and 69% for N+ ultralow-risk breast cancers
Vliek and colleagues (43)	MammaPrint	310	Premenopausal and postmenopausal	N0	None in 79% of ultralow	10-year DR-free interval rate of 96.7% among ultralow-risk breast cancers, mostly (79%) without systemic treatments
Weiser and colleagues (49)	Oncotype DX	45,217	Postmenopausal	N0	None vs. standard ET	No OS improvement by the addition of ET (HR = 1.39; 95% CI, 0.79–2.47) in patients between 50–69 years with RS < 11
Ohnstad and colleagues (46)	PAM50	231	Premenopausal and postmenopausal	N0	None	15-year breast cancer–specific survival of 96.3% among untreated patients with a low ROR

Abbreviations: DR, distant recurrence.

reported in patients who received or did not receive adjuvant ET (although this decision was not randomized; ref. 41).

Consistently, a retrospective population-based analysis of 418 elderly patients with HR+ breast cancer confirmed a similar percentage of ultralow-risk breast cancers (12.0%), with a 10-year distant recurrence rate of 2% in this patient subgroup, even among patients at high risk according to clinicopathological criteria and even in the absence of adjuvant treatments in about half of the cases (42). The excellent prognosis of ultralow-risk breast cancers was additionally reported in the prospective RASTER study. Indeed, this study reported a similar percentage of ultralow-risk breast cancers (13%, $n = 34$), and although 79% of clinically low-risk/genomically ultralow-risk patients with breast cancer did not receive any adjuvant systemic treatment, their excellent prognosis was maintained with a 10-year distant recurrence–free interval rate of 96.7% (43).

The prognosis of patients with genomic ultralow-risk breast cancers receiving de-escalated ET or no ET has also been evaluated retrospectively in a limited number of randomized trials. In particular, among 538 evaluable patients included in the STO trial, a randomized 3-arm study evaluating the benefit of 2 years of tamoxifen versus 5 years of tamoxifen versus no ET in postmenopausal patients with node-negative HR+ breast cancers, the benefit of tamoxifen in terms of breast cancer–specific survival was confirmed both in the MammaPrint low- and high-risk groups, even for patients who received a shorter treatment duration (44). However, a further analysis focused on patients with ultralow-risk breast cancers (15% of cases, $n = 98$) showed that this subgroup presented an excellent clinical outcome, with a 20-year breast cancer survival of 97% among patients treated with tamoxifen and 94% among patients who did not receive any systemic therapy (27).

MammaPrint was also evaluated in a similar setting in the IKA trial, which randomized postmenopausal patients between no adjuvant ET versus a limited duration of adjuvant tamoxifen treatment (1 or 3 years). Among 135 cases analyzed, 23 (17%) were classified as ultralow, and the recurrence-free interval at 10 years was 100% for node-negative ($n = 16$) and 69% for node-positive patients with breast cancer ($n = 7$; **Table 2**; ref. 45).

PAM50

Molecular characterization by PAM50 was also investigated among untreated patients. Among 653 evaluable patients enrolled in the observational Oslo1 trial, 231 patients with node-negative HR+ breast cancer did not receive any adjuvant chemotherapy or ET. About half (53.7%) had a low-risk ROR disease and presented an excellent long-term outcome, with a 15-year breast cancer–specific survival of 96.3% (46).

Beyond its ability to identify patients with excellent long-term prognosis, intrinsic subtype classification has also been assessed as a potential predictor of ET benefit in patients with early HR+ breast cancer. Chia and colleagues analyzed the PAM50 intrinsic subtypes of the tumors of 398 premenopausal patients enrolled in the NCIC CTG MA.12 trial, a prospective randomized trial of tamoxifen versus placebo. Besides confirming the prognostic value of PAM50, the investigators also reported that the luminal subtype by PAM50 was associated with benefit from tamoxifen treatment (HR = 0.52; 95% CI, 0.32–0.86), whereas no statistically significant benefit for the use of tamoxifen was observed in patients with non-luminal tumors (HR = 0.80; 95% CI, 0.50–1.29 for non-luminal subtypes). However, the interaction test was not significant ($P = 0.24$; ref. 47).

More recently, a similar analysis was performed in 437 samples from the SBII:2 pre-trial, which randomized premenopausal women between 2 years of adjuvant tamoxifen or no adjuvant tamoxifen treatment, in the absence of other systemic therapies. In this study, a significant benefit from adjuvant tamoxifen treatment was observed among luminal A breast cancers (HR = 0.41; 95% CI, 0.23–0.74; $P = 0.003$) but not among luminal B breast cancers (HR = 1.19; 95% CI, 0.63–2.27; $P = 0.59$). These data suggest a potential resistance to adjuvant tamoxifen therapy among luminal B breast

cancers in premenopausal women, further refining the ability of PAM50 in predicting ET effect (48).

Other commercially available genomic assays

Very limited data exist for the potential use of other genomic assays to identify subgroup of patients potentially amenable to de-escalation of ET. A retrospective analysis of the National Cancer Database identified 45,217 postmenopausal patients with HR+/HER2− breast cancer with tumors <3 cm N0 and Oncotype DX RS ≤25. Among these, 5.7% of patients (2,585) did not receive adjuvant ET therapy after surgery. A subgroup analysis of this cohort of patients reported no significant improvement in OS with the addition of ET to surgery ($P = 0.40$), even after correction at multivariate analysis (HR = 1.39; 95% CI, 0.79–2.47), in patients between 50 and 69 years of age with a RS < 11 (49). Although intriguing, these analyses are significantly limited by their retrospective nature.

Other Perspectives

This review is specifically focused on available evidence evaluating the potential use of commercially available gene expression assays in the management of adjuvant hormonal therapy. However, the potentialities of transcriptomics in the tailoring of endocrine treatment have been explored well beyond this specific context.

Indeed, a number of different genomic signatures have been developed to assess prognosis and response to endocrine treatment in early HR+/HER2− breast cancer but have not reached commercial availability for use in clinical practice. Among several others, the genomic grade index has been one of the most extensively studied signatures. This signature combines the expression of 97 genes to identify the genomic correlate of histologic tumor grade and has been reported to be able to stratify patients into high and low genomic risk subgroups, which independently predict the prognosis of both untreated and tamoxifen-treated breast cancers (50).

Moreover, transcriptomics also holds potential to address sensitivity to other endocrine agents used in the advanced setting. For example, a number of studies have assessed the potential use of transcriptomics to investigate sensitivity to fulvestrant. In the TransCONFIRM trial, Jeselsohn and colleagues analyzed the association between gene signatures and response to fulvestrant in 134 patients with advanced breast cancer. Although PAM50 and Oncotype DX were not associated with progression-free survival, 37 genes associated with progression-free survival were identified, consisting of genes involved in ER regulation, cell fate, and proliferation (51). Similarly, a 414 gene panel able to predict fulvestrant response in cell lines was developed by Knudsen and colleagues (52) and then further validated in patients treated with neoadjuvant fulvestrant in a phase II trial.

Overall, this wealth of data highlights the still incompletely explored potential of transcriptomics in the tailoring of ET, both in the early and advanced settings.

Discussion

Up to date, the choice of adjuvant ET for patients with breast cancer is still mostly guided by classic clinicopathological features. However, with the growing complexity of treatment scenario, in which both escalation and de-escalation strategies are available, the identification of additional biomarkers to properly stratify patients' risk and sensitivity to ET represents a significant clinical need. In this regard, genomic assays represent an attractive biomarker as they have already proven to be a valuable tool to guide adjuvant chemotherapy decision in early-stage HR+/HER2− breast cancers (53, 54) and have been evaluated with a similar aim in the neoadjuvant setting (55).

On one side, the identification of patients at risk of late recurrences and who could benefit from extended adjuvant ET represents a crucial challenge. Indeed, the benefit demonstrated by extended adjuvant treatment in reducing the long-term risk of recurrence is modest, whereas a significant rate of toxicities was observed (6, 56). The CTS post-5 years (CTS5), combining tumor size, number of nodal metastases, tumor grade, and age at diagnosis, has been developed to estimate the risk of distant recurrence after 5 years of ET in postmenopausal women (57). Additionally, gene expression assays have shown both prognostic and predictive values in this setting, being associated with the risk of late recurrence as well as the benefit of prolonged ET. In particular, several prospective–retrospective randomized control studies independently validated BCI as a predictive biomarker for extended ET, both with AI and tamoxifen treatment. Similar results, even if in a more limited number of studies, have been presented for MammaPrint, identifying MammaPrint high-risk breast cancers as at risk of early recurrence and deriving less benefit from an extended treatment, probably due to a reduced sensitivity to ET. Based on this evidence, both BCI and MammaPrint have reached a level of evidence 1B in this context, and the latest American Society of Clinical Oncology and National Comprehensive Cancer Network guidelines have embraced the use of BCI to guide decision regarding extended ET, both with tamoxifen or AI, in patients with 1 to 3 positive lymph nodes (4, 58). However, these results cannot be extended to all genomic assays as the relationship between high-risk genomic classification and extended ET benefit differ among different tests, highlighting how different genomic assays may depict different biological features of breast cancers. The varying ability of different tests to capture distinct disease behaviors may be partly attributed to differences in the study populations used to develop these tests. For example, MammaPrint was developed within a cohort of patients younger than 55 years, with breast cancer tumors less than 5 cm, predominantly untreated with systemic therapies (40). In contrast, BCI (H/I) was developed within a cohort of patients treated with 5-year tamoxifen therapy (14). These differences might have potentially led to the identification of different biological features in the assays and therefore to a different performance when addressing specific clinical questions.

In addition, the evolution of the adjuvant treatment of HR+/HER2− breast cancers may represent a potential limitation in the applicability of these results. Indeed, CDK4/6 inhibitors (abemaciclib and ribociclib) have proven efficacy in addition to ET as adjuvant treatment of patients with high-risk HR+/HER2− breast cancers, and abemaciclib has been approved for high-risk HR+/HER2− breast cancers (59, 60). There is a lack of data regarding the benefit of extended adjuvant therapy after adjuvant CDK4/6 inhibitors, as well as regarding the potential value of genomic assays to guide ET extension in this setting. Furthermore, in the near future, gene expression assays might potentially be increasingly used to select patients for adjuvant CDK4/6 inhibitors. Indeed, in the NATALEE trial, patients with stage IIA N0 HR+/HER2− breast cancer could be included if the tumors were classified as high–genomic risk, and a number of randomized trials specifically designed to select patients to treat with adjuvant CDK4/6 inhibitors based on gene expression assays are ongoing. In this context, the

phase III ADAPTlate trial (NCT04565054) is evaluating the benefit of 2 years of adjuvant abemaciclib treatment in combination with standard ET among patients with high clinical or genomic risk (defined by Oncotype DX, Prosigna, EndoPredict, or MammaPrint). The ADAPTcycle trial (NCT04055493), instead, is a phase III study enrolling intermediate risk patients (according to Oncotype DX and antiproliferative response to 3 weeks of preoperative ET) and randomizing them to adjuvant ribociclib therapy or chemotherapy. Preliminary data from this trial and the ADAPT trial confirmed that Oncotype DX RS is a strong negative independent predictor for antiproliferative response to preoperatory ET response, both in premenopausal and postmenopausal women, with RS > 25 being associated with lower rates of endocrine response (61). However, these preliminary results also reported that the type of ET (tamoxifen alone vs. tamoxifen + OFS vs. AI + OFS) and RS are both independently associated with antiproliferative ET response, and although very low levels of antiproliferative response (19.5%) were achieved in premenopausal patients with high-risk tumors (RS > 25) with tamoxifen alone, the use of more intensive endocrine treatment (AI + OFS) was able to achieve a high response rate (77.8%) even in these higher-risk patients. These results suggest that the use of Oncotype DX to tailor ET in premenopausal patients should be investigated in larger trials. Finally, some trials are assessing whether gene expression assays might be used as an intermediate endpoint in HR+/HER2− breast cancer; for example, the RIBOLARIS trial is evaluating whether chemotherapy may be avoided among patients with initial high-risk clinicopathological breast cancer who are converted to low–genomic risk assessed by PAM50 after 6 months of neoadjuvant letrozole–ribociclib therapy (NCT05296746). Nevertheless, these studies will not offer additional information regarding the benefit of extended adjuvant therapy after adjuvant CDK4/6 inhibitor and the predictive value of genomic assays in this treatment scenario.

On the other side, the use of ET even for patients with low-risk HR+ breast cancer has significantly increased over the last decades, generating the risk for significant overtreatment in this context. Indeed, in the latest years, clinical trials and guidelines have progressively led to an increase of ET duration as well as to a general shift toward a wider use of AIs (58, 62). Additionally, the introduction and wide diffusion of screening programs has increased the identification of indolent early-stage breast cancer, partially estimated to be overdiagnoses that would have never led to clinical symptoms (63). Despite the fact that ET is generally considered a less toxic treatment compared with chemotherapy, it still carries significant burden of long-term side effects, which has been shown to affect treatment adherence (64). It would be therefore extremely relevant and useful to be able to identify patients with breast cancer with extremely favorable long-term prognosis who could be safely treated only with locoregional therapy and limited or no ET.

Indeed, consistent data from retrospective analyses of clinical trials have shown that genomic assays might be used to identify a small but yet significant proportion of patients with HR+ breast cancer with an extremely low risk of recurrence even in the absence of systemic treatment. These patients, given their excellent prognosis, could benefit from a de-escalation of standard 5-year adjuvant ET in terms of omission of ET or shorter treatment duration. MammaPrint, using the ultralow threshold, has been the most extensively studied assay in this contest, having shown the ability to identify patients with limited benefit from ET in several studies. Despite the difficulties related to the limited number of low-risk patients, the low event rate, and the long follow-up needed, dedicated prospective studies are warrant. The phase II LESS trial is currently recruiting postmenopausal patients with HR+/HER2− breast cancers identified as ultralow-risk according to MammaPrint to receive only 2 years of AI therapy (NCT05297617). Similarly, the phase II LA LEAST trial is currently recruiting patients older than 50 with node-negative HR+/HER2− breast cancers identified as low-risk by PAM50 who will receive a shorter treatment with only 2 years of standard ET (NCT03917082). In this context, a severe limitation is represented by the application of these data to premenopausal patients. Although several studies included premenopausal patients, this subgroup of patients generally constituted a minority of cases, and the prognostic and predictive roles of the various assays specifically according to menopausal status are usually not reported. Therefore, in several cases, the possibility to extrapolate results

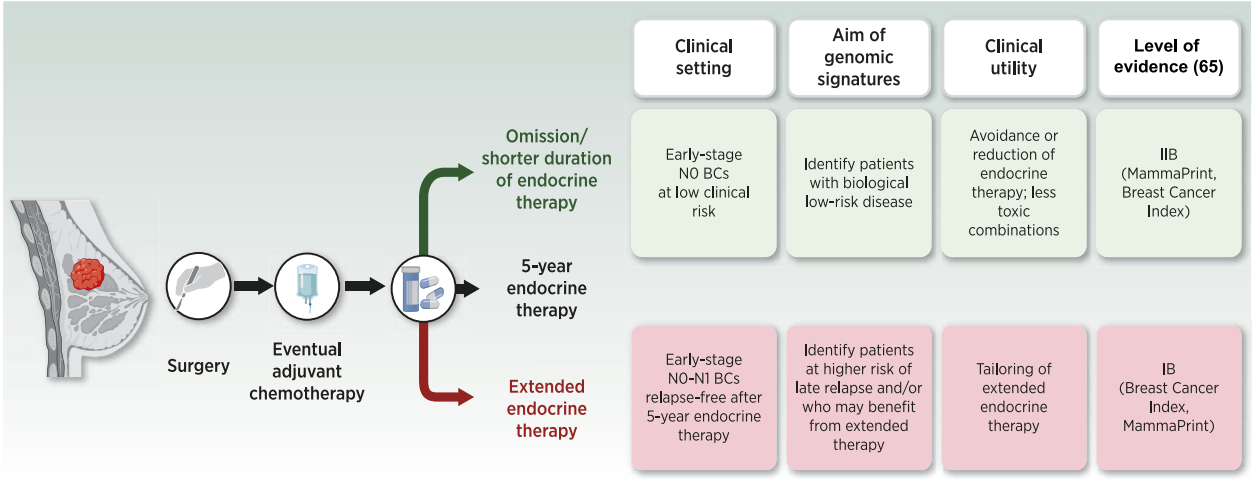

Figure 1.

Applications of genomic signatures in the decision-making process of adjuvant ET of early-stage HR+/HER2− breast cancers. (Adapted from an image created with BioRender.com.) (65).

Table 3. Level of evidence of commercially available genomic signatures according to different applications in the adjuvant setting (in some cases, only the evidence of prognostic role, and not of predictive role, is available).

	Adjuvant chemotherapy	Extended ET	ET de-escalation
Oncotype DX	IA	IIC	Limited data
MammaPrint	IA	IB	IIB
PAM50	IB	IIB	Limited data
BCI	IB	IB	IIB[a]
EndoPredict	IB	IIB	No data

[a]Association of BCI (H/I)-low with benefit from OFS in premenopausal patients.

obtained in a prevalently postmenopausal patient population to premenopausal patients still remains to be explored and confirmed.

With this growing body of evidence supporting new applications of genomic assays and prospective trials ongoing, a further challenge should be acknowledged. Genomic assays could become an important tool for aiding in the management of all main moments of adjuvant treatment of early-stage HR+/HER2− breast cancers, from the prescription of chemotherapy to the choice of ET and its potential prolongation with an extended treatment (**Fig. 1**). This could lead to a further expansion of approval and reimbursement of genomic assays from the current scenario of intermediate-risk patients to a potentially wider group of patients. In this perspective, it should always be kept in mind that different genomic assays might not present the same prognostic abilities when applied to different clinical questions in different clinical settings (**Table 3**). Therefore, a comprehensive evaluation of the data supporting the use of each test for each specific clinical question is crucial and will represent a research priority for the coming years.

Conclusions

In conclusion, gene expression assays are emerging as a potentially useful tool to personalize adjuvant ET through the tailoring of this duration and type. Although significant evidence has been acquired for the use of BCI to guide decision regarding extended ET leading to its inclusion in the American Society of Clinical Oncology and National Comprehensive Cancer Network guidelines, available evidence for the use of gene expression assays to guide ET de-escalation in ultralow-risk patients still remains limited, mostly based on retrospective analyses of a limited number of studies. Therefore, there is an urgent need for dedicated prospective trials to confirm these results, with the objective of further optimizing adjuvant treatment strategies in patients with HR+/HER2− breast cancer by sparing unnecessary treatment-related toxicities.

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