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Hot Topic

Gene-expression signatures to inform neoadjuvant treatment decision in HR+/HER2− breast cancer: Available evidence and clinical implications

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ABSTRACT

Over the last few years, the indication for chemotherapy use in HR+/HER2− early BC has been significantly modified by the introduction of gene-expression profiling. In the adjuvant setting, several gene-expression signatures have been validated to discriminate early stage HR+/HER2− BC with different prognosis and to identify patients for which adjuvant chemotherapy can be spared. Considering their ability to optimize the choice of adjuvant treatment and the increasing use of neoadjuvant approach in early BC, the potential use of gene-expression signatures to discriminate patients to be candidate to neoadjuvant chemotherapy or endocrine treatment appears particularly appealing. Indeed, the San Gallen Consensus Conference panel recently endorsed the use of genomic assays on core biopsies as a potential strategy for choosing the type of neoadjuvant treatment (chemotherapy or endocrine therapy) in selected patients. In this context, we here review evidence supporting the use of most common commercially available gene-expression signatures (Oncotype DX, MammaPrint, PAM50, EndoPredict and Breast Cancer Index) in patients receiving neoadjuvant therapy for HR+/HER2− BC. Data on the association of gene expression signatures and response to neoadjuvant chemotherapy or neoadjuvant endocrine therapy will be reviewed and the clinical implications of this data to guide the clinical decision-making process in early HR+/HER2− BC will be discussed.

Introduction

Initially implemented in clinical practice for the treatment of locally advanced breast cancer (BC) patients, the use of neoadjuvant treatment has progressively increased over the last decades and is nowadays considered the standard of care for many early BC patients as well [1,2]. In this context, neoadjuvant chemotherapy (NCT) is widely used to downstage initially operable BCs, increasing the rates of conservative surgery [3]; however, it is well-known that the magnitude of response to NCT varies significantly according to breast cancer subtype. Pathological complete response (pCR) rates are, in fact, much lower in hormone receptor-positive/HER2−negative (HR+/HER2−) BC (7–16%) as compared to triple negative or HER2+ tumors (30–50%). The CTNeoBC pooled analysis not only highlighted that HR+/HER2− BC appears to be less chemosensitive than other BC subtypes, but also pointed out that a significant heterogeneity in response to NCT exists within this subtype. Indeed, grade 1–2 HR+/HER2− BC presents even lower pCR rates (6–9%) as compared to grade 3 HR+/HER2− BC (13–19 %) [4].

Although traditionally reserved for elderly patients or for patients considered unfit for chemotherapy, neoadjuvant endocrine treatment (NET) has proven to be an effective and safe strategy for HR+/HER2− BC in postmenopausal women, with clinical results in terms of clinical responses and conservative surgery rates comparable to NCT [5,6]. Despite representing a compelling and less toxic treatment alternative, the role of NET is less established and selection of appropriate patients remains controversial. To date, guidelines recommend the use of NET for postmenopausal patients with HR+/HER2− BC without a clear indication for chemotherapy [7] or for low-risk luminal biology based on clinical characteristics and/or genomic signatures [1].

Indeed, the indication for chemotherapy use in HR+/HER2− early BC has been significantly modified by the introduction of gene expression profiling. In the adjuvant setting, several gene expression signatures have been validated to discriminate early stage HR+/HER2− BC with different overall prognosis and to identify patients at low-risk of relapse

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for which chemotherapy can be omitted [8,9]. Moreover, the recent presentation of the randomized RxPONDER trial, which demonstrated that postmenopausal women with one to three positive lymph nodes and low-risk by genomic signatures (21-gene recurrence score of ≤ 25), derive no further benefit from the addition of chemotherapy to endocrine therapy, has further expanded the number of patients for which chemotherapy might potentially be spared [10].

Considering their ability to optimize the choice of adjuvant treatment and the increasing use of neoadjuvant approach in early BC, the potential use of gene expression signatures to discriminate patients to be candidate to neoadjuvant chemotherapy or endocrine therapy appears particularly appealing. The feasibility of using core biopsy of BC for transcriptional profiling has been assessed in several studies [11–14]; moreover, a recent study evaluating the agreement of the 21-gene expression signature between core biopsies and paired surgical specimens without neoadjuvant systemic therapy has confirmed a significant degree of concordance [15]. In this context, the San Gallen Consensus Conference panel recently endorsed the use of genomic assays on core biopsies as a strategy for choosing the type of neoadjuvant treatment (chemotherapy or endocrine therapy) in selected patients [16].

Here, we review the evidence supporting the use of most common commercially available gene-expression signatures (Oncotype DX, MammaPrint, PAM50, EndoPredict and Breast Cancer Index) in patients receiving neoadjuvant therapy for HR+/HER2− BC, with a particular focus on data on the association of gene expression signature results and response to NCT or NET. Moreover, the clinical implications of this data to guide the clinical decision-making process in early HR+/HER2− BC will be discussed.

Oncotype DX recurrence score and response to neoadjuvant treatment

High Oncotype DX recurrence scores are associated with higher pCR rates in HR+/HER2− BC patients treated with NCT

The Oncotype DX 21-gene recurrence score assay is the most extensively studied signature in this context. The 21-gene Recurrence Score was first reported to be associated with the likelihood of pCR by Gianni et al. in 2005 [17] and the association between Oncotype DX and pCR has been subsequently confirmed by a number of studies (Table 1).

Recently, a systematic metanalysis of seven studies involving 1744 patients further confirmed the association between pretreatment recurrence score and pCR. In this metanalysis, 777 patients out of 1744 had a high recurrence score (45%), defined as > 25 or > 30 according to study definition. The pCR rate was significantly higher in patients with high recurrence score as compared to patients with low-intermediate

Table 1
Published studies reporting the association between Oncotype DX Recurrence Score and pathologic complete response in HR+/HER2− breast cancer patients receiving neoadjuvant chemotherapy.

Authors	RS subgroups	Patients in each subgroup	pCR rates	p-value (RS as categories)	Odds Ratio RS as categories (95% C.I.)	p-value (RS as a continuous)	Odds Ratio RS as a continuous (95% C.I.)
Gianni et al. (2005) [17]	NR	89	12.4%	NR	NR	p = 0.005	NR
Mina et al. (2006) [57]	NR	45	13.3%	NR	NR	p = 0.67	NR
Chang et al. (2008) [58]	<18	8	0%	NR	NR	p = 0.008	Ref.
	>30	42	21.4%				1.7 (1.15–2.60)
Yardley et al. (2015) [59]	<18	19	0%	p = 0.030	NR	NR	NR
	18–30	17	0%				
	>30	24	17%				
Pivot et al. (2015) [60]	<18	29	0%	p = 0.004	NR	NR	NR
	18–30	28	6.2%				
	>30	24	8.6%				
Soran et al. (2016) [61]	<18	27	0%	NR	NR	NR	NR
	18–30	10	0%				
	>30	23	0%				
Iwamoto et al. (2016)[62]	<18	751	4.6%	Ref.	Ref.	NR	NR
	18–30	384	5.7%	p = 0.983*	0.99 (0.27–3.48)*		
	>30	238	16.5%	p = 0.073*	2.61 (0.94–8.02)*		
Pease et al. (2019) [63]	<18	227	2.2%	p < 0.001	1.48 (0.46–4.79)*	NR	NR
	18–30	450	1.6%		Ref		
	>30	312	9.6%		4.87 (2.01–11.82)*		
Kantor et al. (2019) [64]	<11	160	4.4%	p < 0.01	NR	NR	NR
	11–25	612	1.3%				
	>25	605	7.8%				
Thekkekara et al. (2019)[65]	≤25	40	0%	NR	NR	NR	NR
	>25	70	16%				
Mazo et al. (2020) [66]	NR	813	8.1%	NR	NR	p < 0.0001	1.84 (1.44–2.35)
Soliman et al. (2020) [67]	NR	764	7.7%	NR	NR	p = 0.0041	1.42 (1.12–1.80)
Kuemmel et al. (2020)[68]	≤25	153	7.2%	p = 0.006	NR	NR	NR
	>25	423	16.1%				
Murillo et al. (2020) [69]	11-25°	20	0%	NR	NR	p = 0.005*§	0.946 (0.901–0.993)*§
	>25	40	12.0%				
Pardo et al. (2021) [70]	<18	56	10.7%#	p = 0.0268#	NR	NR	NR
	18–30	62	9.7%#				
	>30	40	27.5%#				
Sella et al. (2021) [71]	≤25	38	5.3%	p = 0.09	NR	p = 0.01	1.07 (1.01–1.12)*
	>25	38	21.1%				

*at multivariate analysis.
Axillary pCR.
° RS 20 was used as cutoff for premenopausal patients.
§ calculated for RCB 0-1.

score (11% versus 1%; RR 4.47 95% CI 2.76–7.21, p < 0.001) [18].

Low Oncotype DX recurrence scores are associated with higher clinical response rates in HR+/HER2− BC patients treated with NET

Only a limited number of trials have assessed the association between pretreatment recurrence score and response to NET [19]. We identified three publications reporting Oncotype DX analysis conducted on pre-treatment samples of HR+/HER2− BC patients receiving NET with aromatase inhibitors in the context of prospective clinical trials (Table 2). Taking into account the very low pCR rate observed with NET, all three studies evaluated clinical response to NET (using RECIST or WHO criteria). The largest of these three trials, the TransNEOS trial, prospectively validated the feasibility of RS assay in predicting clinical response after 6 months of neoadjuvant letrozole in 295 ER+/HER2− postmenopausal patients. Clinical response rates among patients with RS < 18 were 54%, significantly higher than in patients with RS > 30 (22%, p < 0.001), and RS group was also significantly associated with the rate of breast-conserving surgery (BCS) [20].

Consistently, a recently published metanalysis of all three trials reported a numerically higher clinical response rates for patients with low genomic risk BC (Oncotype DX RS < 18; clinical response rate ranging from 55 to 64%) and lower clinical response rates for patients with high genomic risk BC (Oncotype DX RS > 30; clinical response rate ranging from 20 to 31%) and confirmed that a significantly higher rate of partial responses is achieved by NET in patients with Oncotype DX RS < 25 or < 30 as compared to patients with higher Oncotype DX RS scores (Odds ratio 4.60, 95% CI 2.53–8.37, p < 0.001 and Odds Ratio 3.40, 95% CI 1.96–5.91, p < 0.001; respectively) [19].

Beyond clinical response, biological response to NET (as assessed by decrease of Ki67 to values ≤ 10% after 2–3 weeks of endocrine treatment with aromatase inhibitors) has also been reported as highly predictive of long-term good prognosis in patients with HR+/HER2− BC [21]. In the prospective WSG-ADAPT HR+/HER2− trial, N0/N1 early BC who were candidates for adjuvant chemotherapy based on clinical-pathological criteria received 3 (±1) weeks of preoperative induction endocrine treatment. Among 386 patients with complete data for Ki-67 at both baseline and post-induction, RS distribution was 23.1% RS 0–11, 58.3% RS 12–25, and 18.7% RS 26–100. Endocrine proliferation response (post-induction Ki67 ≤ 10%) occurred in 84.3%, 76.0%, and 36.1% of these RS groups, respectively, with significantly higher rates in RS 0–11 and significantly lower rates in RS 26–100 as compared to other RS groups (p < 0.001) [22].

Oncotype DX recurrence scores to select neoadjuvant treatment in HR+/HER2− BC patients

A small number of pilot trials have been conducted specifically to test the hypothesis that the 21-gene RS assay could be used to guide the decision to treat with NET versus NCT.

A first small phase II trial enrolled 66 patients with resectable HR + BC for RS testing, of which 46 were evaluable for efficacy analysis (41% had clinically node positive disease). The 21-gene RS was assessed on the initial diagnostic biopsy: patients with RS < 11 received NET (exemestane +/- goserelin for 6 to 12 months), patients with RS > 25 received NCT (docetaxel-cyclophosphamide for 6 cycles), while patients with RS 11–25 were randomized to NET or NCT. As expected, no patients in the RS < 11 and RS 11–25 (both in the NET and NCT treated arm) achieved pCR, while 22% of patients with RS > 25 treated with NCT achieved a pCR [23].

A second phase II enrolled 64 HR+/HER2− BC patients considered not suitable for breast conserving surgery (size ≥ 2 cm). Oncotype DX RS was assessed on core needle biopsies: patients with RS < 11 received NET, patients with RS > 25 received NCT, while patients with RS 11–25 were randomized to NET or NCT. Consistently with the previous study, also in this trial no patients in the RS < 11 and RS 11–25 (both in the NET and NCT treated arm) achieved pCR, while 14% of patients with RS > 25 treated with NCT achieved a pCR. Successful breast-conserving surgery was achieved for 75% of tumors with RS < 11 receiving NET, 72% for RS 11–25 receiving NET, 64% for RS 11–25 receiving NCT, and 57% for RS > 25 receiving NCT and clinical response rate was 83%, 50%, 73% and 93% in the four groups, respectively [24].

Moreover, Oncotype DX RS < 31 or > 26 has been used as selection criteria to include patients in several studies testing the addition of targeted therapy (Cdk inhibitors, everolimus) to NET [25,26].

PAM50 Prosigna and response to neoadjuvant treatment

PAM50 Luminal A subtype is associated with lower pCR rates in HR+/HER2− BC patients treated with NCT

Intrinsic subtype classification of breast cancer in five subtypes Luminal A, Luminal B, HER2−enriched, Basal-like, and Normal-like using microarray-based gene expression analysis was initially reported in 2000 by Perou et al. [27]. Intrinsic subtype assignment using 50 representative genes, also called PAM50, was subsequently developed [28] and introduced into clinical practice as Prosigna (Veracyte Inc., South San Francisco, California, USA). The association between intrinsic subtypes and response to NCT within HR+/HER2− patients was first described by Prat et al. in a combined dataset of 451 patients, showing higher pCR rates among non-Luminal tumors compared to Luminal tumors (30.0 % vs. 8.9 %, adjusted OR = 4.20, 2.220–7.942) [29]. Moreover in 2016, Prat et al. reported that both Prosigna Risk of Recurrence (ROR) (p = 0.047) and intrinsic subtype (Odds Ratio for Luminal A vs. non-Luminal A = 0.341, P = 0.037) were significant predictors of response to NCT in a multicenter cohort of 216 HR+/HER2− BC patients treated with anthracyclines and taxanes [13]. Similar results were observed by Ohara et al. in a cohort of 124 HR+ BC patients treated with neoadjuvant sequential taxanes and anthracyclines. In this study, tumors classified as Luminal A by PAM50 showed

Table 2
Published studies reporting the association between Oncotype DX Recurrence Score and clinical response (clinical complete response plus clinical partial response) in HR+/HER2− breast cancer patients receiving neoadjuvant endocrine treatment.

Author (Year)	RS subgroups	Patients in each subgroup	Response rates (cCR + cPR)	p-value (RS as categories)	Odds Ratio RS as categories (95% C.I.)	p-value (RS as a continuous)	Odds Ratio RS as a continuous (95% C.I.)
Akashi-Tanaka et al. (2009) [72]	<18	11	64%	p = 0.11	NR	NR	NR
	18–30	16	31%				
	>30	16	31%				
Ueno et al. (2014) [73]	<18	32	59%	Ref.	Ref	p = 0.042	0.205 (0.044–0.946)
	18–30	17	59%	p = 0.970	0.977 (0.296–3.233)		
	>30	15	20%	p = 0.017	0.171 (0.040–0.728)		
Iwata et al. (2018) [20]	<18	157	55%	p < 0.001	NR	p < 0.001*	0.06 (0.02–0.18)*
	18–30	84	42%				
	>30	54	22%				

*at multivariate analysis.

the lowest pCR rate (1.9%) and PAM50 Luminal A subtype was a significant (P = 0.031) predictor of non-pCR at multivariate analysis independently of other clinicopathological parameters. Interestingly, this was only observed with gene-expression defined subtypes, but not when IHC surrogate intrinsic subtypes were used [30]. Consistently, a retrospective analysis of microarray data from 253 HR+/HER2− BC patients treated with NCT consistently observed a significantly higher percentage of Luminal A tumors among patients with Residual Cancer Burden (RCB) categories III (63%) and II (55%) than among patients with minimal residual disease (RCB 0/I; 23%) (P < 0.001) and an higher percentage of Basal-like tumors among patients with RCB 0/1 (32%) than among patients with RCB II (8%) and III (6%) [31].

Two other NCT-based trials, the I-SPY 1 and the PROMIX trials, also reported a significant association between PAM50 Luminal A subtype (as compared to other subtypes) and the presence of residual disease after NCT [32,33]. However, these results might at least in part be influenced by the fact that in these two trials gene-expression data from HR+/HER2− and triple-negative BC patients were jointly analyzed.

PAM50 non-Luminal subtypes are associated with reduced biological response to NET in HR+/HER2− BC patients

PAM50 intrinsic subtyping has also been reported to be associated with clinical and biological response to treatment in HR+/HER2− BC patients receiving NET. In the ACOSOG Z1031 trial, which randomized 377 postmenopausal women with clinical stage II to III ER-positive breast cancer to receive neoadjuvant exemestane, letrozole, or anastrozole, PAM50 analysis identified non-luminal subtypes (HER2−enriched or basal-like) in 3.3% (7/213) of patients, all of which showed persistently high surgical Ki67 after treatment with aromatase inhibitors. Moreover, while clinical response and surgical outcomes were similar in Luminal A versus Luminal B tumors, Luminal A BCs showed an higher rate of PEPI score 0 (best prognostic group; 27.1% versus 10.7%; p = 0.004) [34].

A similar study by Dunbier et al. reported the biological effect of 2 weeks of anastrozole in 104 postmenopausal women with ER + BC. Both Luminal A and Luminal B tumors showed a similar proportional Ki67 suppression (mean Ki67 suppression of 75.5% vs 75.5%), while Basal-like and HER2−enriched tumors showed poorer responses (15.3% increase and 50.7% suppression, respectively). Moreover, pre-treatment ROR score was significantly correlated with two week change in Ki67 (Rs = 0.35, p = 0.0019) and with the objective clinical response rate (p = 0.03) [35].

More recently, we reported that in the phase II LETLOB trial [36] which randomized 92 postmenopausal HR+/HER2− BC patients to receive letrozole plus lapatinib/placebo non-luminal PAM50 intrinsic subtyping (Basal-like and HER2−enriched; 26%, N = 17/66) was associated with significantly lower objective response rates (47% vs 78%, p = 0.031) and significantly higher Ki67 levels at surgery (median 10% vs 7%, p = 0.004) as compared to luminal subtypes [37].

Moreover, PAM50 intrinsic subtype has been used as selection criteria to include patients in trials comparing CdK4/6 inhibitors plus endocrine treatment and chemotherapy in the neoadjuvant setting [38,39].

PAM50-based score to predict response to NET and NCT in HR+/HER2− BC patients

Building on the idea that the main driver of chemotherapy sensitivity and endocrine therapy sensitivity is the Basal-like and Luminal A intrinsic biology, respectively, and based on the inverse relationship of endocrine and chemotherapy sensitivity, Prat et al. developed a Chemo-Endocrine Score (CES) based on Correlation Coefficients (CC) to the Luminal A and Basal-like centroids of the PAM50 classification algorithm (CES = CC to Luminal A –CC to Basal-like). CES's predictive ability was then evaluated in 4 independent neoadjuvant data sets and 4 adjuvant data sets of HR+/HER2− patients. In the neoadjuvant setting, CES proved to predict response both to NCT and NET, independently of known clinical-pathological variables. In terms of survival outcome, CES chemotherapy-sensitive group was associated with poor relapse-free survival in patients with ROR-intermediate disease treated with either adjuvant endocrine therapy only or no adjuvant systemic therapy, but not in patients treated with (neo)adjuvant chemotherapy [40]. A similar association between CES and response to NET and NCT (combined with HER2−targeted therapy) has also been described in HR+/HER2+ BCs [41].

MammaPrint and response to neoadjuvant treatment

High risk tumors are associated with higher pCR rates in HR+/HER2− BC patients treated with NCT

MammaPrint is a 70-gene signature that classifies patients into High Risk and Low Risk subgroups based on the risk of distant recurrence at 5 and 10 years. Although the genes detected and the techniques differ between Oncotype DX and MammaPrint, these two gene panels have shown significant agreement in the outcome predictions for individual patients, probably as the result of the tracking of similar biologic characteristics [42]. BluePrint is a molecular profile that integrates the expression levels of 80 genes to determine intrinsic molecular subtypes: Luminal-type, HER2−type and Basal-type. The integration of BluePrint with MammaPrint can further stratify Luminal cancers into Luminal A-type cancers (Low Risk) and Luminal B-type cancers (High Risk) [43].

A number of studies have evaluated the association between MammaPrint subgroups (often integrated with BluePrint) and pCR rates (Table 3). Despite only the two largest studies, Nunes et al. [44] and Whitworth et al. [45], reported a significant increase in pCR rates with the increase in MammaPrint risk (pCR 13% in High Risk vs 2% in Low Risk patients), a similar trend was consistently described in all studies and the lack of significance of most studies may be related to the limited number of patients enrolled.

Moreover, in the I-SPY1 trial 138 patients, unselected for receptor subtypes, were further stratified into "high-risk" and "ultra-high risk" subgroups. A significantly higher percentage of pCR after NCT was found among the "ultra-high risk" subgroup (33% vs 15%, p = 0.038) and TN and HER2+ BCs were more frequent in this population [46]. These results, suggesting a potential additional MammaPrint score stratification, were further validated in the I-SPY2 trial. In this adaptive phase II trial, the addition of durvalumab and olaparib to standard chemotherapy increased pCR rates from 22% to 37% in HER2− BC patients classified as High-Risk patients according to MammaPrint. An exploratory analysis in the HR+ /HER2− subtype group suggested ultra-high MammaPrint status as a potential predictive marker of benefit of durvalumab/olaparib over chemotherapy alone, with a pCR rate of 64% compared with 22% in the control arm [47].

MammaPrint and response to NET

Very limited data is available regarding the predictive role of MammaPrint and BluePrint to NET. In the Neoadjuvant Breast Registry Symphony Trial (NBRST), 474 HR+/HER2− BC patients were classified into four molecular subgroups by MammaPrint/BluePrint subtyping (Luminal A, Luminal B, HER2−type, and Basal-type). Of these, 69 patients were treated with NET (the majority with an aromatase inhibitor, 7 patients with tamoxifen); all but one patient had a BluePrint Luminal tumor. 68% of patients treated with an aromatase inhibitor and 29% of patients treated with tamoxifen had a clinical response, with similar clinical response rate among Luminal A tumors (MammaPrint Low Risk) and Luminal B tumors (MammaPrint High Risk) (68.6% and 66.7%, respectively) [45]. More recently, Jacobs et al. reported similar results describing the efficacy of NET among 51 Low Risk patients according to MammaPrint. Radiologic response was 76%, and 7 of 11 patients in

Table 3
Published studies reporting the association between Mammaprint risk groups and pathologic complete response in HR+ (or Luminal by Mammaprint) breast cancer patients receiving neoadjuvant chemotherapy.

Authors	MammaPrint subgroups	Patients in each subgroup	pCR rates	p-value MP as categories (95% C.I.)	Odds Ratio MP as categories (95% C.I.)	p-value MP as a continuous (95% C.I.)
Straver et al. (2010)° [74]	Low Risk	23	0%	p = 0.07	NR	NR
	High Risk	106	15%			
Krijgsman et al. (2012)§[43]	Low Risk	29	3%	NR	NR	NR
	High Risk	53	11%			
Gluck et al. (2013)§ [75]	Low Risk	90	6%	NR	NR	NR
	High Risk	154	10%			
Whitworth et al. (2014)§[76]	Low Risk	44	2%	NR	NR	NR
	High Risk	145	7%			
Bayraktar et al. (2014)§[77]	Low Risk	15	7%	NR	NR	NR
	High Risk	44	5%			
Whitworth et al. (2017)[45]	Low Risk	95	2%	p = 0.385*	1.922 (0.420–9.438)*	p < 0.001*
	High Risk	310	13%			
Nunes et al. (2019) [44]	Low Risk	120	2%	p = 0.0015	NR	NR
	High Risk	235	13%			

°Includes HR+/HER2+ patients.
§Includes Luminal BC according to Blueprint.
*At multivariate analysis.

whom mastectomy was initially indicated became eligible for BCS after NET [48].

Using MammaPrint to choose neoadjuvant therapy (ongoing trial)

The use of MammaPrint as a tool to choose neoadjuvant therapy is currently under evaluation in the phase II prospective "PersonaLized neoAdjuvant Strategy ER Positive and HER2 Negative Breast Cancer TO Increase BCS Rate" (PLATO) study. Its primary end point is the rate of BCS in patients with HR+/HER2− BC for whom BCS is not feasible. In this study, all patients are initially tested with MammaPrint: if classified as high-risk according to MammaPrint, patients will receive NCT; if classified as low-risk, patient will be treated with NET (letrozole, with the addition of leuprorelin in premenopausal patients) [49].

Other commercially available gene-signatures and response to neoadjuvant treatment

EndoPredict is a 12-gene assay developed to predict the likelihood of distant recurrence in ER+/HER2−BCs.

An association between EndoPredict and pCR was first described in 553 ER+/HER2− BCs treated with NCT. EndoPredict signature, both as categorical and continuous variable, was significantly correlated with pCR, with a lower pCR rate in the low-risk group compared to the high-risk group (7% vs 17%, respectively, $p < 0.001$) [50]. More recently, similar results were observed by Dubsky et al. in 134 HR+ patients treated with NCT in the ABCSG-34 trial. None of the 9 low-risk patients exhibited RCB 0-I, while 33 of 125 (26.4%) high-risk patients exhibited RCB 0-I after NCT. In the same study, 83 patients were treated with NET. When treated with NET, more patients with low-risk disease (12/44; 27.3%) had RCB 0-I compared with those with high-risk disease (3/39; 7.7%) [51].

Breast Cancer Index is a genomic assay that analyses the expression of 7 genes and stratifies BCs in 3 risk groups (Low, Intermediate and High risk). The ability of the Breast Cancer Index to predict chemosensitivity was retrospectively evaluated among 150 BCs of all subtypes treated with NCT. Risk stratification according to Breast Cancer Index in the 94 patients with ER+/HER2− tumors was significantly associated with pCR ($p = 0.0492$) and breast conserving surgery ($p = 0.0162$) [52].

Clinical implications

In patients with HR+/HER2− early breast cancer, gene expression signatures are extensively used as a tool to aid decision making regarding the use of adjuvant chemotherapy and a number of different molecular assays profiles are now commercially available. However, the potential application of gene expression signatures to predict response to NCT and NET for HR+/HER2− BC patients and therefore inform neoadjuvant treatment decision still remains partially unexplored.

Available data, reviewed in this paper, points out that a consistent association between higher risk (as assessed by gene expression signatures) and higher pCR rate after NCT was observed across different gene expression assays. Symmetrically, an association between lower risk (as assessed by gene expression signatures) and higher response rate after NET was observed across different gene expression assays (Fig. 1). Despite these promising observations, which are also consistent with the limited benefit observed from the use of adjuvant chemotherapy in HR+/HER2− BC patients with low risk gene expression assays, we should acknowledge that the available evidence in this context, especially for patients treated with NET, remains scarce and the conduction of larger prospective trials to confirm these results should be advocated. Moreover, it is well known that different gene-expression signatures are not completely superimposable and not all available commercial gene expression assays present the same quantity/quality of evidence concerning their association with response to neoadjuvant treatment; caution should therefore be used if choosing a specific assay in this context.

Given the small sample size of most studies and the absence of clear criteria to decide which patients might be tested, there is a lack of consensus regarding the routine use of gene expression assays to decide neoadjuvant treatment in HR+/HER2− BC. The San Gallen Consensus Conference recently endorsed genomic assays on core biopsies as a strategy for choosing which type of neoadjuvant therapy (chemotherapy or endocrine therapy) to pursue in patients who might benefit from treatment response to optimize surgery in the preoperative setting. The vast majority (98%) of the panel voted in favor of NET for postmenopausal HR+/HER2− BC patients with low-grade and/or low-genomic signature tumors with an indication for neoadjuvant treatment and a majority of panelists (73%) considered that genomic assays, where available, could be performed on the core biopsy specimen to aid in this decision. On the other hand, the ASCO guideline Expert Panel recommended against the use of genomic profiles to guide clinical decision making regarding neoadjuvant treatment given the lack of prospective randomized trials directly addressing this issue [16,53]. Moreover, an algorithm based on ER, PgR and Ki67 expression at baseline and after 2–4 weeks of AI treatment has also been proposed as an alternative method to select patients for NET [54].

In this context of uncertainty, several considerations are in order and

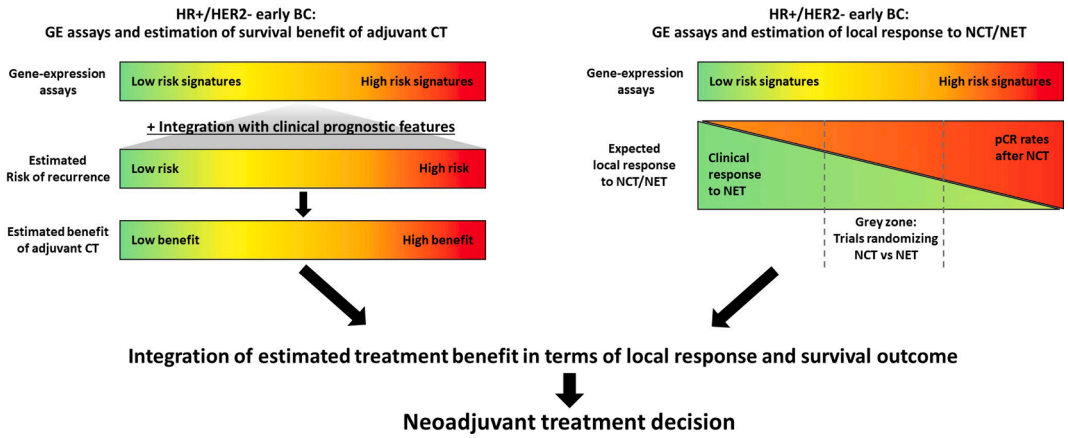

Fig. 1. Potential of gene-expression signatures to inform neoadjuvant treatment decision.

can help guide the clinician in neoadjuvant treatment decision in early HR+/HER2− BC.

First, the potential use of gene expression assays to inform neoadjuvant treatment decision between NCT and NET mostly applies to post-menopausal patients, as for premenopausal patients there is a paucity of data for NET and this should not be routinely recommended outside clinical trials [7]. Moreover, based on the results of TAILORx and RxPONDER trials, the use of different cutoffs for the OncotypeDX assay have been proposed for postmenopausal (or aged $\geq$ 50) and premenopausal women with HR+/HER2− BC. This might at least in part limit the potential field of application of gene expression assays for premenopausal women even if, whether these differences might be partially explained by the endocrine effect of chemotherapy through the induction of ovarian suppression, still remains to be completely elucidated [8,9,55]. In fact, evidence that chemotherapy exerts an anti-estrogenic biological effect on tumor samples from pre-menopausal patients has recently been presented, thus supporting the hypothesis that a substantial proportion of the benefit of chemotherapy in pre-menopausal women may be related to its ability to induce an endocrine effect, most likely through a decrease in estradiol levels secondary to ovarian function suppression [56].

Second, the use of gene expression assays in the neoadjuvant setting might potentially inform clinical decision in two ways (Fig. 1). On one hand, the integration of their results with clinical prognostic features might help estimate more precisely the potential risk of recurrence of the patient and therefore the potential benefit expected from chemotherapy use, extrapolating from the consolidated evidence available in the adjuvant setting. However, we should be well aware that adjuvant trials testing the use of gene expression assays (such as the RxPONDER and MINDACT trial) only included surgically staged patients with up to three positive lymph nodes. Therefore, extreme caution is needed when trying to apply these results in the neoadjuvant setting where only limited information regarding nodal involvement (especially for what concerns number of positive nodes) can be obtained through imaging and post-neoadjuvant pathological staging might be altered by treatment effect.

On the other hand, when considering the short-term benefit of neoadjuvant treatment in terms of tumor response and potential conversion to breast-conserving surgery, data for small sized studies reviewed in this paper might suggest that low risk tumors by gene expression assays might benefit more from NET as compared to high risk tumors by gene expression assays which achieve higher pCR rates with NCT. These observations, integrated with other clinicopathologic data, might potentially be useful for the clinician to define the best multidisciplinary clinical pathway for each single patient. However, we caution that this is not sufficient evidence per se to omit neo/adjuvant chemotherapy in low risk by gene-expression assays HR+/HER2− BC patients, outside the boundaries of evidence produced by large adjuvant phase III trials.

Conclusions

In conclusions, considering the ability of gene-expression assays to optimize the choice of adjuvant treatment and the increasing use of neoadjuvant approach in early BC, the potential use of gene expression signatures to select the type of neoadjuvant treatment (chemotherapy versus endocrine) appears worth exploring. To date, available evidence in this context is mostly based on small sized retrospective studies and not all available commercial gene expression assays present the same quantity/quality of evidence concerning their association with response to neoadjuvant treatment.

Therefore, there is an urgent need for larger prospective trials to confirm these results and further optimize neoadjuvant treatment strategies in HR+/HER2− BC patients who present with tumors that are suboptimal for breast conservative surgery.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: GG reports personal fees from EliLilly and Novartis, outside the submitted work. MVD reports Eli Lilly, MSD, Exact Sciences, Novartis, Pfizer, Seagen, outside the submitted work. VG reports Roche, Novartis, Eli Lilly, MSD, GSK, Gilead, outside the submitted work. The remaining authors declare no competing interests.

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