



REVIEW ARTICLE

Genomic assays for lobular breast carcinoma

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ABSTRACT

Background: One of the current challenges in breast cancer is the appropriate treatment of invasive lobular breast cancer (ILC) and defining the high-risk group within ILC. The biological character of ILC typically translates to a good prognosis, however, several studies have indicated that the long-term prognosis is worse than for patients diagnosed with the more commonly invasive ductal carcinoma. Many genomic tests are now available to determine whether those patients are at high risk (HR) and enable tailored treatment. Unfortunately, most of the studies in which these genomic tests have been evaluated entail retrospective analysis of a prospective trial.

Aim: This review focuses on the validation of the available genomic assays based on trials performed in ILC patients, where in some instances, the various subtypes of ILC (classical, pleomorphic, and non-classic type) were taken into account.

Results: Using Oncotype DX in retrospective studies, only 1.3%–8% of ILC tumors were categorized as HR tumors. For MammaPrint, 24% of patients were classified as HR, which was associated with poor outcome. In a recent sub-analysis of the MINDACT study comprising 487 ILC patients, 16.2% were high genomic risk. EndoPredict, Prosigna Breast Cancer Prognostic Gene Signature Assay, and the Breast Cancer Index have been validated in patients receiving only endocrine treatment.

Conclusion: Although ILC accounts for the second most common breast cancer subtype in women, none of these tests encompass tumor morphology in their algorithms. Prospective studies on ILC with genomic assays are warranted given the various subtypes of and treatment options for this underestimated, but frequently occurring cancer.

Relevance for Patients: Genomic assays can be employed in ILC patients to predict the risk of recurrence and identify those patients who might benefit from chemotherapy in addition to their standard treatment regimen.

1. Introduction

Breast cancer (BC) is the most prevalent cancer in women. Every year over 2 million new cases are diagnosed and this cancer type is responsible for the highest number of cancer-related deaths among women [1]. Treatment of BC has evolved, resulting in better survival rates. However, BC is heterogeneous and each subtype has its own particularities that require a specific therapeutic approach. Most clinical data have been gathered for invasive ductal carcinoma (IDC), commonly referred to as “no special” type, which comprises 75% of the invasive BCs. Invasive lobular carcinoma (ILC) is the second most common histological subtype, representing about 10% of invasive BCs and ranks as the 6th most common cancer in women [2].

Most ILCs are estrogen receptor (ER) positive, HER2 negative, and tend to have a lower grading (84% Grade 2) with the absence of vascular invasion [3,4]. In contrast to IDC, the absolute benefit of adding chemotherapy (CT) to endocrine treatment (ET) of early

stage ILC is controversial because of the minimal added value [5]. Furthermore, the percentage of complete pathological response rate (pCR) in the neoadjuvant setting is substantially lower in ILC than in IDC (6.2% vs. 17.4%, $P < 0.001$) [6]. ILC can be highly metastatic, and the overall long-term outcome of ILC patients in a large study was worse than those diagnosed with IDC. This paper in part aims to underscore that ILC is a separate entity in the spectrum of BCs, which exacts a more personalized approach to identify patients at high risk of recurrence [7]. Furthermore, different ILC subtypes have been described on the basis of their morphology and cytology [8]. The classical type of ILC is associated with a good overall prognosis, whereas the pleomorphic subtype, characterized by lower expression of hormone receptors and a higher rate of HER2 expression, is associated with worse prognosis [4,9,10].

Several risk calculators and scoring systems have been developed, such as PREDICT and the Nottingham Prognostic Index (NPI) [11,12]. Clinicopathological features are incorporated in these scoring systems, but they do not accurately reflect the histological subtype and cannot be used as the only tool for clinical decision making in a particular case. Nowadays, genomic testing has increased diagnostic resolution and made personalized medicine possible. Several assays are commercially available, such as Oncotype DX [13], MammaPrint [14], genomic grade analysis [15], Prosigna Breast Cancer Prognostic Gene Signature Assay (PAM50) [16], EndoPredict (EPclin) [17], and the Breast Cancer Index (BCI) [18].

Most prospective trials using genomic assays validated recurrence scores without distinguishing between the different histological profiles of BC. Consequently, ILC is underrepresented and leaves clinicians with no clear understanding about the optimal management. In this review, we will evaluate the role of genomic assays in patients diagnosed with ILC.

2. Oncotype DX

At present, the Oncotype DX breast recurrence score (RS) uses 21 specific genes and is the most widely used prognostic assay in the United States. This assay is recommended for hormone receptor-positive, HER2-negative, and node-negative early stage BC [19]. Recently, its utility in node-positive early BC (1 – 3 lymph nodes) was investigated [20-22].

The Oncotype DX test calculates a RS from 0 to 100 and categorizes patients as low risk (LR, score of <18), intermediate risk (IR, score of 18 – 30), or high risk (HR, score of >30). To further validate the RS, prospective trials (TAILORx and RxPONDER) are now being completed using less restrictive cutoffs to minimize undertreatment, as were the case with the traditional RS cutoffs (LR, RS of 1 – 10; IR, RS of 11 – 25; and HR, RS of >26).

Several randomized trials demonstrated that BC patients, not specifically ILC, with high RS benefitted from adjuvant CT, whereas those with low RS did not [21,23]. The effect of adjuvant CT in patients with IR remained uncertain. TAILORx (Trial Assigning Individualized Options for Treatment) was set up as a prospective randomized trial with 6,711 node-negative patients

with an RS ranging from 11 to 25. Invasive disease-free survival (DFS) rates following CT + ET or ET alone were compared [13]. Similar outcomes for both therapeutic regimens were observed in postmenopausal BC patients with IR, although some benefit from CT + ET was seen in women aged 50 or less and an IR in the upper range (Table 1).

The results of the RxPONDER (treatment for positive node, endocrine responsive breast cancer) trial have been published recently [25]. This Phase 3 study randomized hormone receptor-positive and HER2-negative patients with an RS of 25 or lower to ET only or to CT + ET with a follow-up of 5.1 years. No benefit was seen in postmenopausal women ($P = 0.82$) with an RS of ≤ 25 , but premenopausal women exhibited a 46% reduction in the risk of invasive disease with the addition of CT (94.2% vs. 89.0%, hazard ratio = 0.54, $P = 0.004$). However, in premenopausal women, ovarian suppression was performed in 15.9% of patients in the CT arm, which could indirectly improve the outcome in those patients, and led to a 5-year overall survival (OS) absolute improvement of 1.3%.

Some retrospective studies have examined the role of Oncotype DX testing in the management of patients with ILC as presented in Table 2. In general, the RS of most ILC cases tended to be in the low-to-intermediate range and only 1 – 2% of the included patients had a high RS.

The first study conducted by Conlon *et al.* examined the RS by Oncotype DX in 135 of a total of 878 patients diagnosed with ILC at their institution during 2008 – 2011. In the 135 studied patients with ILC, 63% had an LR, 35.5% had an IR, and 1.5% had an HR. Most of the patients with classic ILC (cILC, $N = 108$; 68%) had an LR score. IR was found in 32% of the patients and none had an HR. On the contrary, patients with pleomorphic ILC (pILC, $N = 13$)

Table 1. Chemotherapy benefits according to age and RS

Age	RS 0 – 15	RS 16 – 20	RS 21 – 25	RS 26 – 100
>50 years	No CT benefit	No CT benefit	No CT benefit	Substantial CT benefit
≤50 years	No CT benefit	1.6% CT benefit	6.5% CT benefit	Substantial CT benefit

Data obtained from Sparano *et al.* [24]. CT: Chemotherapy, RS: Recurrence score

Table 2. Overview of Oncotype DX scores in ILC

References	ILC (N)	LR (%)	IR (%)	HR (%)	cILC-pILC (%)	FU (m)	BCSS/OS (%)
Conlon <i>et al.</i> [26]*	135	63	35.5	1.5	80 – 10	47	98.5/-
Felts <i>et al.</i> [27]*	102	42	56	2	80 – 13	55	89/92***
Tsai <i>et al.</i> [28]*	158	57	42	1.3	79 – 9	-	-
Kizy <i>et al.</i> [29]**	7,321	21	71	8	-	74	>95/-
Weiser <i>et al.</i> [30]**	15,763	20.5	72.9	6.6	-	60	-/83****

*RS cutoffs: LR (score of ≤ 18), IR (score of 18 – 30), and HR (score of >30). **TAILORx RS cutoffs: LR (score of 1 – 10), IR (score of 11 – 25), and HR (score of >25). ***Pure ILC (pILC excluded). ****N0 disease 5-year OS rate: LR 96.9%, IR 97.0%, and HR 94.4% ($P = 0.0003$). N1 disease 5-year OS rate: LR=95.5%, IR=95.5%, and HR=83.8% ($P = 0.0004$). ILC: Invasive lobular cancer, LR: Low-risk recurrence score, IR: Intermediate-risk recurrence score, HR: High-risk recurrence score, cILC: Classic ILC, pILC: Pleomorphic ILC, FU: Follow-up, BCSS: Breast cancer-specific survival, OS: Overall survival, N: Number, m: Months

had an LR score in only 2 of 13 cases (15%). In 9 of 13 patients (70%), the RS was intermediate and 2 had an HR (15%). Bias in this study is probable because only 15% of the treated ILCs were tested. The tested tumors proved to be smaller and more node negative than the not Oncotype DX tested ILC tumors. In this study, patients with IR were treated more frequently with adjuvant CT than patients in the LR group (54% vs. 18%, $P < 0.0001$). The patients in the LR group who had undergone adjuvant CT were significantly younger and were more likely to have positive lymph nodes. The RS played a role in decision-making regarding CT in approximately 74% of the cases [26].

The second study by Felts *et al.* retrospectively analyzed 102 patients diagnosed with early stage ILC during 2001 – 2011. The patients were compared to 307 patients with early stage IDC. Most of the ILC patients were reported as LR (42%) and IR (56%), and only 2% were HR. For the IDC population, the risk score pattern was 55.7%, 35.2%, and 9.1%, respectively. A difference between the subtypes was also found in the grade distribution ($P = 0.0046$) and RS ($P = 0.03$). The cILC group had more Grade 1 and LR tumors than the two other subtypes, although one cILC tumor was Grade 3 and HR. Kaplan–Meier survival curves showed that DFS for ILC varied significantly with histological subtype ($P = 0.049$) and tumor stage ($P = 0.0025$). The 5-year DFS was 100% for pILC, 89% for cILC, and 43% for mixed subtypes, but the DFS for the pILC and even more for the mixed subtypes dropped far below the DFS for cILC after 5 years. The same was true for the 5-year OS, which was 100% for pILC, 92% for cILC, and 73% for mixed subtypes. After 5 years, the OS for pILC and the mixed subtypes became less than for cILC ($P = 0.018$) [27].

The third study by Tsai *et al.* was a retrospective study to predict uniformly low Oncotype DX RS using histologic tumor characteristics [28]. Oncotype DX testing of 158 ILC patients resulted in a distribution with 57% LR, 42% IR, and 1.3% HR. The analytical model showed that progesterone receptor (PR) was the most important factor followed by Ki-67 positivity to distinguish low from high RS. This approach may therefore be useful in predicting low recurrence risk in ILC, with a sensitivity of 92.3%, a specificity of 97.7%, and a correct classification of 96.5%.

A more recent study by Kizy *et al.* analyzed the Surveillance, Epidemiology, and End Results (SEER) database from 2004 to 2013 to determine the impact of adjuvant CT on long-term survival of patients with ILC. Using the TAILORx RX cutoff, 21% of 7316 patients were classified as LR, 71% were IR, and 8% were HR. Adjuvant CT was given to 8% of LR, 19% of IR, and 58% of HR patients. The 5-year breast cancer-specific survival (BCSS) was 99% for the LR patients, 99% for those in the IR group, and 96% for the HR group. Patients in the HR score cohort were more likely to die compared to LR patients (hazard ratio 2.37). In this trial, adjuvant CT did not seem to yield a survival benefit for both the IR and HR cohorts [29].

Tadros *et al.* prospectively examined in the Genomic Health Clinical Laboratory from February 2004 to August 2017, where 610,350 tumor specimens and RS were compared among the histological subtypes [31]. Significant diversity was found in

terms of RS results in patients with special histological subtypes (ILC, IDC + ILC, IDC + other, and ILC + other), with a lower mean RS than was seen for IDC. In the whole population, most patients had a low RS (59.2%), and only 9.5% had a high RS. Patients with ILC had a lower mean RS than patients with IDC (16.3 vs. 18.4), but this study did not evaluate the impact of RS on prognosis or CT benefit in non-ductal carcinomas.

There are no prospective trials using the Oncotype DX RS in ILC, but the classification of Oncotype DX testing in risk scores might help to identify those at intermediate and high risk of ILC recurrence. In this context, the study by Christgen *et al.* warrants addressing. In a prospective clinical trial (WSG PlanB trial), 353 lobular cancers (14% of the patients studied), and 2,232 (86%) non-lobular cancers were retrospectively analyzed. Although the percentage of patients with high RS was 3 times lower in lobular than in non-lobular BC (8% vs. 24%, $P < 0.01$), the 5-year DFS estimates for lobular and non-lobular BC were similar (92.1% vs. 92.3%, not significant). In the subsequent multivariate analysis, prognostic parameters for DFS in lobular BC were histological Grade 3 and nodal stage pN3 but not Oncotype DX RS. Therefore, the prognostic value of RS in lobular BC seems to be different from that in non-lobular BC [32].

Recently, Weiser *et al.* validated the Oncotype DX RS in ILC using the National Cancer Database. A lower percentage of high RS was identified in ILC compared to IDC, defined as RS > 25 (6.6% vs. 16%, $P < 0.001$). In ILC, 10% less CT was prescribed in patients with high RS with either N0 or N1 disease, compared to similar patients diagnosed with IDC. Furthermore, an absolute OS benefit was correlated with CT in high RS patients (4.2% absolute 5-year OS advantage in N0 disease and 12.2% OS advantage in N1 disease). This study clearly demonstrated that Oncotype DX RS is a valid prognostic tool for ILC patients [30]. Furthermore, Makower *et al.* evaluated the Oncotype DX RS in non-ductal BC. As previously reported, a lower incidence of high RS in tumors with lobular histology was observed. ILC was most likely coupled with an intermediate RS of 11 – 25. OS for IDC and ILC was similar, whereas mixed histologies (ductal + lobular) were associated with improved OS. Adjuvant CT was associated with improved OS in IDC ($P < 0.0001$). Although the study concluded that benefit of adjuvant CT was limited to patients with IDC, the benefit of CT in ILC patients with an RS of > 26 cannot be excluded [33].

3. MammaPrint

The second test, MammaPrint by Agendia, was initially developed from whole-genome expression arrays (25,000 genes) of BC specimens [34]. It is a prognostic assay that measures the mRNA expression of 70 genes and stratifies patients as genomic “low risk” or “high risk” in terms of developing distant metastases. Several validation studies have been performed in a population of node-negative BC not receiving adjuvant therapy [35-37].

A large Phase III prospective clinical study, the Microarray in Node-negative and 1 – 3 positive lymph node Disease may Avoid Chemotherapy (MINDACT) trial, validated the MammaPrint assay. A total of 6693 patients with early BC were enrolled, but

only early Stage T1-2, N0-1 patients with discordant clinical and genomic risk (N = 2,187) were assessed and randomized for CT [14]. In the group of patients with high clinical risk features, 46% were classified as genomically low risk by MammaPrint. This specific group was randomized for CT, but no significant benefit of CT on DFS, OS, and survival without metastasis was observed. Therefore, adjuvant CT could be avoided in those patients [38].

The prognostic value of MammaPrint for ILC was validated in the study by Beumer *et al.* A total of 217 early-stage ILC patients from five clinical studies were included in the study. Twenty-four percent were assigned to the HR group. This percentage is much higher than the one reported for the studies evaluating Oncotype DX, which may be attributed to the application of the test in a different population. MammaPrint HR status in ILC was 2.1 times more often associated with distant metastases or death within 10 years after surgery. Moreover, in a sub-analysis of the lymph node-negative ILC subgroup, the MammaPrint HR group had a 11 times higher likelihood of an event and 5.1 times higher chance to die within 10 years after surgery. These results are indicative of the value of MammaPrint in risk determination, specifically in lymph node-negative ILC [39].

An update of the MINDACT study, presented as an abstract at the European Breast Cancer Conference by Metzger *et al.* in 2020, focused on MammaPrint testing in ILC in comparison to IDC. Following general classification, 487 patients were diagnosed with ILC (255 cILC and 232 ILC variants) and 4826 patients were diagnosed with IDC. In general, ILC tumors were larger and more often ER positive and HER2 negative. Nodal involvement (N1-N3) was similar. Clinically, 48.3% of the ILC and 51.5% of IDC were HR, whereas MammaPrint classified 16.2% of the ILC and 39.1% of the IDC as genomically HR. Within the ILC group, 10.2% of cILC and 22.8% of ILC variants were genomically high grade. A discordance in the risk classification of ILC was observed in 6% of patients being clinically low risk but genomically high risk and in 38% of patients with a clinically high-risk and genomically low-risk constellation. Distant metastasis-free survival (DMFS) and DFS were similar for ILC and IDC classified as either low or high genomic risk (Table 3) [40]. The patient population included in both studies was heterogenous and featured HER-2-positive and ER-negative patients.

A recent study identified 2610 patients with ILC who underwent MammaPrint testing using the National Cancer Database. Overall, 280 patients (11%) were classified as high genomic risk. Five-year OS rates were worse for patients classified as HR (83% vs. 94%, $P < 0.05$). These patients were associated with a greater probability

of death (hazard ratio 2.07) when compared to low genomic risk. However, the study did not identify which patients would benefit from adjuvant CT based on the MammaPrint profile [41].

4. EndoPredict (EPclin)

The EPclin, offered by Myriad Genetics, is a genomic test based on the expression of 12 genes. In combination with clinical features of the tumor (size and nodal status), the risk score is either low risk or high risk of BC recurring as distant metastases within 10 years after diagnosis [17].

In a cohort of 869 consecutive patients with early hormone receptor-positive and HER2-negative BC, EPclin was performed in 156 (18%) of the patients. In the group of patients with IDC (N = 121), 44% were LR and 56% were HR. In the ILC group (N = 24), this was 46% and 54%, respectively [42].

The prognostic value of EPclin in ILC was assessed using the data of three large clinical trials (ABCSG-6, ABCSG-8, and TransATAC) by Sestak *et al.* [43]. A cohort of 470 postmenopausal women with N0 and N+ ILC who had been treated with ET was analyzed (Table 4). The EPclin proved to be more prognostic than the Clinical Treatment Score, which is based on clinicopathological characteristics only (HR = 2.17, 95% CI = 1.73 – 2.72). In the ILC group, 63.4% of women were LR and exhibited a 10-year distant recurrence (DR) of 4.8%, while 36.6% of patients was HR with a DR risk of 26.6%. Using the EPclin risk score, the 10-year DR in case of ILC and IDC was similar in both LR and HR groups. In women with lymph node-positive disease (N = 144), 26.4% were categorized as LR by EPclin, with the remaining women as HR (73.6%). Significantly higher 10-year DR risk was observed for patients in the EPclin HR group compared those in the LR group (31.2% vs. 6.4%). It should be underscored that these results are only applicable to women who had received ET only.

5. Prosigna Breast Cancer Prognostic Gene Signature Assay (Formerly PAM50)

PAM50 encompasses a quantitative reverse-transcription polymerase chain reaction based on the expression of 50 genes. The test subsequently provides risk mRNA-based risk stratification to assess a patient's risk of DR at 10 years in postmenopausal early stage, hormone receptor-positive patients.

Validation of the PAM50 test was performed with patients in the Danish Breast Cancer Group database. The Prosigna algorithm calculates the molecular subtype (luminal A, luminal B, HER2 enriched, or basal like) and calculates a risk of recurrence (ROR) score (1 – 100 scale) based on a 46-gene subset of the 50 target genes (PAM50), with inclusion of a proliferation score (mean expression of an 18-gene subset of the 50 genes) and tumor size.

Table 4. The value of EPclin in ILC and IDC

EPclin	ILC (N = 470)	10-year DR (%)	IDC (N=1,994)	10-year DR (%)
EndoPredict low	63.4%	4.8	59.1	
EndoPredict high	36.6%	26.6	40.9	

DR: Distant recurrence. Data obtained from Sestak *et al.* [43]

Table 3. Overview of MammaPrint scores in ILC

References	ILC (N)	MammaPrint HR (%)	MammaPrint LR (%)	DMFS/ DFS (%)
Beumer <i>et al.</i> [39]*	127	24	76	-
Metzger <i>et al.</i> [40]	487	16.2	83.8	95.5/90.8
Jenkins <i>et al.</i> [41]**	2,610	11	89	-

*In lymph node-negative cases: MammaPrint HR 18%, MammaPrint LR 82%. **OS: HR 83%, LR 94%. DMFS: Distant metastasis-free survival, DFS: Disease-free survival, HR: High risk, LR: Low risk

Follow-up data were collected of all patients (N = 2558) diagnosed from 2000 to 2003 with ER-positive and HER2-negative BC receiving 5 years of ET. Patients with IDC (N = 1570) had 1–3 positive lymph nodes or a tumor size of >20 mm. The PAM50 ROR showed a statistically significant association with the 10-year DR rate. An analysis for BC with special histological subtype, such as apocrine and medullary tumors, showed identical results [44].

In another study using the same cohort of patients (Danish Breast Cancer Group database, 2000–2003), a group of 341 patients with ILC was identified. Included patients had ER-positive and HER2-negative BC, having a tumor size of > 20 mm or 1–3 positive lymph nodes, and were scheduled for ET during 5 years [45]. A significantly higher number of ILC cases was assigned to the group with a low ROR compared to the IDC cases (41% vs. 22%, $P < 0.0001$). Table 5 summarizes the corresponding data. Ninety-seven (28%) ILC patients were IR and 104 (31%) were HR. In patients with ILC and low PAM50 the 10-year DR rate was 7.7%, whereas this was only 3.5% for those diagnosed with low PAM50 IDC. In the intermediate and high ROR group, the risk of a DR event was significantly higher for both ILC and IDC. This study showed that patients with ILC had significantly poorer 10-year DR compared to patients with IDC in the same ROR score group. Thus, these results could affect treatment decisions regarding the addition of CT to ET for women with ILC.

6. Breast Cancer Index (BCI)

The BCI, provided by Biotheranostics, analyzes the activity of seven genes to help predict the risk of hormone receptor-positive, N0-1 BC recurring 5–10 years after diagnosis. Furthermore, the BCI predicts the benefit of extended ET in patients with early-stage, hormone receptor-positive BC [46]. BCI reports two results: (1) How likely the cancer is to come back 5–10 years after diagnosis and (2) whether the patient is likely to benefit from taking ET for a total of 10 years. The U.S. Food and Drug Administration has not yet approved the BCI.

This test combines the gene expression profiles of the HOXB13/IL17BR ratio (H: I) and the Molecular Grade Index (MGI). It is the only validated, commercially available test with data demonstrating the prognostic risk up to 15 years. H: I is linked to dysfunctional estrogen signaling in BC, and MGI is a five-gene signature that recapitulates tumor grade [47]. Extending the duration of adjuvant ET has been validated in BCI patients included in the Adjuvant Tamoxifen-To offer more (aTTom) randomized trial. BCI by high H: I expression was predictive of an endocrine response and identified a subset of hormone receptor-positive and node-positive patients who benefitted for 10 years instead of 5 years from tamoxifen treatment (10.2% absolute risk

reduction, $P = 0.027$) [48]. Other trials also demonstrated benefit from extended ET, supporting the need for an individualized patient selection that the BCI offers [48-50].

The clinical utility of BCI in ILC has been analyzed and presented at San Antonio Breast Cancer Symposium in 2019. The study included 311 ILC patients (99% ER positive, 52% Stage T1, 42% node positive, and 66% Grade II) with 10 years of median follow-up. In this study, 53% of patients were classified as BCI low/intermediate risk and 47% of patients were classified as HR. The overall 10-year risk of DR was significantly different in the low/intermediate and HR groups (6.0% vs. 27.9%) [51]. These results demonstrate that a substantial portion of ILC was associated with a high 10-year risk of DR and late DR, as illustrated in Table 6.

In a second study, BCI results for hormone receptor-positive and lymph node-negative BC (N = 2,554) were compared between ILC patients (13.7%) and IDC patients (80.7%). The analysis revealed that the median BCI score was lower in ILC than in IDC ($P < 0.0001$) and classified a smaller fraction of patients as high risk for late DR compared to IDC (36.5% vs. 53.1%; $P < 0.0001$) [52]. Furthermore, a slightly decreased proportion of patients with ILC was identified as benefitting from extended ET compared to IDC (38.2% vs. 41.1%).

7. GenomicG (GG)

The GG is a 97 gene-comprising assay developed and validated with the purpose of assessing tumor grading more objectively in IDC [15]. Histological grading (HG) suffers from inter- and intra-observer variability. The therapeutic assessment of low-grade (G1) tumors and high-grade (G3) tumors tends to be different. Most ILCs are classified as intermediate (G2) and therapeutic implications become vague. By applying the GG, a better reclassification is possible as a result of which most HG2 tumors could be attributed to either a low (GG1) or high GG category (GG3) [53].

Metzger-Fihlo *et al.* studied 166 ILC samples (87% cILC and 13% pILC) [54]. The HG classification for Grades 1, 2, and 3 was 20%, 73%, and 7%, respectively. Using the GG, the problematic group of HG2 was reduced: 64% for GG1, 19% for GG2, and 17% for GG3. The percentage of HG and GG for cILC and pILC is presented in Table 7. In the median follow-up time of 6.5 years, the 5-year invasive DFS and OS of the GG3 tumors were less than for GG1 tumors, confirming the modeling that underlies this genomic test. Nodal status, tumor size (only for invasive DFS), and GG2/GG3 were significant prognostic factors for invasive DFS and OS, whereas the histological subtype (cILC or pILC) was not. This is in contrast with the study of Iorfida *et al.*, which found differences in DFS and OS for the different ILC subtypes.

Table 5. Value of Prosigna-PAM50 in terms of predicting 10-year DR and OS in ILC and IDC

ROR	ILC (N = 341)	10-year DR (%)	10-year OS (%)	IDC (N = 1,570)	10-year DR (%)	10-year OS (%)
Low ROR	41%	7.7	82	22%	3.5	87
Intermediate ROR	28%	18	70	29%	9.7	81
High ROR	31%	28.1	68	49%	20.8	66.6

Data obtained from Laenholm *et al.* [45]. DR: Distant recurrence, OS: Overall survival, ROR: Risk of recurrence.

Table 6. 10-year DR in BCI low-/intermediate- and high-risk cohort

BCI	ILC (N = 311)	10-year DR (%)	Early DR (%)	Late DR (%)
BCI low/intermediate	53%	6	1.4	5.6
BCI high	47%	27.9	11.8	18.2

Data obtained from Sella *et al.* [51]. DR: Distant recurrence

Table 7. Distribution of HG and GG according to lobular histology

Grade	ILC (N = 166)		cILC (N = 144)		pILC (N = 22)	
	GG	HG	GG	HG	GG	HG
Grade 1	20%	64%	22%	69%	5%	27%
Grade 2	73%	19%	74%	15%	68%	46%
Grade 3	7%	17%	4%	16%	27%	27%

Data obtained from Metzger-Filho *et al.* [54]. cILC: Classic ILC, pILC: Pleomorphic ILC, HG: Histological grade, GG: Genomic grade

Worst outcomes were found for solid ILC and mixed non-classic ILC versus patients with cILC [8].

Another study reclassified 83% of the ILC tumors (N = 118) into low or high grade. Eighty-one percent of the HG2 (N = 96) were reclassified. In total, 72% of cILC patients were GG1, 14% were GG3, while 14% remained undetermined [55]. In the subset of pILC (N = 13), GG was able to reclassify the majority of the HG2 tumors: 38.5% became GG1, 23% were classified as GG3, while 38.5% remained Grade 2. The prognostic value of GG for invasive DFS was demonstrated for the subset of node-negative ILCs (N = 57; GG1 vs. GG3; hazard ratio 0.24; $P = 0.03$), but not for the overall series.

8. LobSig

A recently developed 194-gene signature was capable of stratifying the prognosis in ILC (LobSig) [56]. LobSig is the first gene signature with a primary focus on prognostication of ILC patients and outperformed the NPI, Prosigna, Oncotype Dx, and GG in a stepwise, multivariate Cox proportional hazards model, particularly in Grade 2 tumors. LobSig high tumors were associated with a high prevalence of ERBB2 (20.0%), ERBB3 (14.3%), AKT1 (8.6%), and ROS1 (8.6%) mutations, paving the way for the employment of targeted therapies. The signature, however, needs further validation in ILC cohorts.

9. Discussion

It has been demonstrated that ILC differs from IDC in its pathophysiology, genetic alterations, patient characteristics, and treatment offered in daily practice [7,57]. A cardinal feature of ILCs is the absence of E-cadherin, causing incohesive proliferation [58]. Most ILC cases are luminal A, but pleomorphic and apocrine lobular carcinomas tend to be luminal B, whereas some are HER2-positive and belong to HER2-enriched subgroups [8]. The majority of the ILC tumors expresses ER and ILC patients strongly benefit from ET [7]. The survival of most ILC patients is good compared to IDC patients, although survival results are surprising when follow-up periods extend beyond 5 – 10 years. The outcome after

10 years became worse for ILC patients [59]. The development and implementation of genomic assays will contribute to more accurate and personalized patient care by identifying those who could benefit from the addition of CT to their treatment [60]. However, most prognostic studies on BC have been performed on patients with predominantly ductal cancers; their validity in patients with ILC, therefore, lacks substantial credence.

Both Oncotype DX and MammaPrint have been extensively validated for BC in general and are used as such. Oncotype DX testing is restricted to hormone receptor-positive, HER2-negative, and N0-1 tumors. The MINDACT study design for MammaPrint also rendered hormone receptor-negative and HER2-positive tumors eligible for analysis, but in practice nearly all of these tumors were classified as high risk.

The interest for ILC is new and no prospective randomized trials have been conducted to date. Using Oncotype DX testing, several studies included a rather low percentage of high-risk ILC tumors, with TAILORx cutoffs ranging from 1.5% – 2.0% or 6.6% – 8.0%. Bias in the Oncotype DX studies by, for example, restrictions on the study population has been discussed. Several studies revealed the same low HR percentage in ILC. Recently, Weiser *et al.* used the National Cancer Database to validate the use of RS in ILC. The authors concluded that far less patients with ILC have a high RS and those with HR were treated with CT, although CT was less often administered compared to similar IDC patients (17.3% vs. 24.6%; $P < 0.0001$) [30]. These findings may be explained by clinical trials demonstrating that patients with ILC experienced no benefit from the addition of CT to their treatment regimen [61]. However, an absolute OS advantage was positively correlated with the receipt of CT by patients with ILC and a high RS, with pronounced benefit in case of node-positive disease. In contrast, Kizy *et al.* and Chen *et al.* demonstrated that ILC patients with a high RS did not benefit from CT [28,62].

Current data on risk classification in ILC using the MammaPrint are scarcer. Beumer *et al.* found that MammaPrint was significantly associated with OS and DMFS among patients with ILC [39]. Metzger *et al.* also reported that MammaPrint was associated with DFS among patients with ILC [40]. The largest study that evaluated the prognostic and predictive value of MammaPrint for patients with ILC found that the assay was significantly associated with survival, but failed to predict the benefit of adjuvant CT in patients with high genomic risk [41].

EPclin, PAM50, and the BCI have been validated in patients receiving ET, an obvious and valid option given that ILC is hormone sensitive. Certain particularities should be remembered, however. The EPclin RS has been validated for ET only as adjuvant therapy in both lymph node-negative and -positive patients [43]. In case of PAM50 ROR, tumors were more than 20 mm or had 1 – 3 positive lymph nodes [45]. The BCI is not approved yet, but it provides additional information on a late DR and an extended ET [51]. The HR groups amounted to 36.6% of all ILCs for EPclin, 31% for PAM50, and 36 – 47% for BCI, solely to emphasize the fact that the reported percentage of HR ILC tumors by Oncotype DX is low. However, the number of studies and patients for these three tests still pale in comparison to those for Oncotype DX and MammaPrint.

The genomic grade panel has been shown to be more powerful to reclassify HG to GG1 or GG3 and was able to recategorize some pILC to the lower risk category and some cILC to the higher risk group [7,55]. In a multivariate Cox proportional hazards model, the GG2/GG3, nodal status, and tumor size (only for invasive DFS) were prognostic factors for DFS and OS.

Different subtypes of ILC have been reported to play a role in survival. A poorer prognosis for pILC – the solid and the mixed non-classic variants, has been demonstrated using traditional pathology sections [8]. In the study by Conlon *et al.*, pILC but not cILC presented with high Oncotype DX RS, although numbers were very limited [26]. Felts *et al.* found a significant difference in Oncotype DX RS for pILC versus cILC and tumor stage [27]. DFS and OS beyond the 5-year mark were worse for pILC and perhaps surprisingly even worse for the mixed subtypes of ILC. In the update of the MINDACT study on ILC, 10.2% of cILC and 22.8% of ILC variants were genomically HG within the ILC group. Arguments have been posited that the subtype of ILC might play a role in determining prognosis, but it is unclear whether characteristics such as HER2 positivity or PR negativity, being more prevalent in pILC, constitute underlying causes.

10. Concluding Remarks

The clinical utility of genomic predictors for adjuvant CT decision-making in luminal breast cancer has been demonstrated, however, ILC has received little attention. In ILC patients, the time between diagnosis and relapse/recurrence can be long, making prospective studies difficult to sustain. Therefore, most studies were at best a retrospective analysis of a prospective trial and comprise a limited number of patients. In addition, several genomic tests are only applicable in tumors with specific restrictions, such as hormone receptor positivity, HER2 negativity, and ET only. Being aware of these limitations and caveats, the majority of genomic tests were able to define a seemingly relevant high risk group for ILC, but comparisons and definite conclusions remain difficult at this stage. Future research should entail a prospective design considering the various subtypes of this underestimated cancer.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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