Prognostic Value of EndoPredict in Women with Hormone Receptor–Positive, HER2-Negative Invasive Lobular Breast Cancer

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ABSTRACT

Purpose: Invasive lobular carcinoma (ILC) accounts for approximately 5%–15% of all invasive breast cancer cases. Most of the correlations between multigene assays and patient outcome were derived from studies based on patients with invasive ductal carcinoma (IDC) or without distinction between the subtypes. Here, we investigate the prognostic value of EndoPredict (EPclin) in a large cohort of ILCs pooled from three phase III randomized trials (ABCSG-6, ABCSG-8, TransATAC).

Experimental Design: The primary objective of this analysis was to determine the prognostic value of EPclin for distant recurrence (DR) in years 0–10 in postmenopausal women with ILC. The primary outcome was DR.

Results: 470 women (17.9%) presented with ILC, 1,944 (73.9%) with IDC, and 216 (8.2%) with other histologic types. EPclin was highly prognostic in women with ILC [HR = 3.32 (2.54–4.34)] and provided more prognostic value than the Clinical Treatment Score [CTS; HR = 2.17 (1.73–2.72)]. 63.4% of women were categorized into the low EPclin risk group and they had a 10-year DR of 4.8% (2.7–8.4) compared with 36.6% of women in the high-risk group with a 10-year DR risk of 26.6% (20.0–35.0). EPclin also provided highly prognostic information in women with node-negative disease [HR = 2.56 (1.63–4.02)] and node-positive disease [HR = 3.70 (2.49–5.50)].

Conclusions: EPclin provided highly significant prognostic value and significant risk stratification for women with ILC. Ten-year DR risk in the EPclin low-risk groups were similar between ILC and IDC. Our results show that EPclin is informative in women with ILC and suggest that it is equally valid in both histologic subtypes.

Introduction

Invasive breast cancer is a heterogeneous disease with specific morphologies and phenotypic features (1). The majority of breast cancers are invasive ductal carcinoma (IDC; around 80%), followed by invasive lobular carcinoma (ILC; 5%–15%), and less than around 8% are tumors with other specific or special histologic features (apocrine, medullary, mucinous, papillary). ILC tumor cells are typically round, small, relatively uniform, noncohesive, and have a characteristic growth pattern characterized histologically as single-file infiltration of the stroma. Inactivation of E-cadherin (*CDH1*) by mutation, loss of heterozygosity, or methylation are characteristic molecular changes in ILC, particularly the pleomorphic subtype (2). Outcome varies by histologic subtypes, with ILC typically presenting with favorable features associated with good prognosis, such as estrogen receptor (ER) positivity, low to intermediate grade, low Ki67 expression, and absence of *HER2* amplification (3).

Approximately 85% of women with ER-positive invasive disease remain recurrence free after 10 years, suggesting that the majority of patients are overtreated. Several multigene assays have been evaluated for the prognostication of early-stage invasive ER-positive breast cancer and have shown clinical utility for the likelihood of risk of recurrence (4–8). However, the development and validation of these assays have been mostly performed in women without considering histologic subtype and little is known about the performance of these assays specifically in ILCs. EndoPredict (EPclin) covers several cellular processes, such as proliferation, apoptosis, DNA repair, cell adhesion, and cell signaling, and combines the expression of proliferative and ER signaling–associated genes with information on nodal status and tumor size (9–11). This combined algorithm is used as a diagnostic test in the clinical setting. EPclin has been validated as a prognostic test in pre- and postmenopausal women with ER-positive, HER2-negative breast cancer (6, 10, 12, 13). More recently, EPclin has been evaluated for the prediction of chemotherapy benefit in a combined analysis of five large clinical trials (14).

Here, we evaluate the ability of EPclin to predict distant recurrence at 10 years specifically in women with ILC and compare the prognostic performance to women with IDC.

Materials and Methods

2,630 postmenopausal women with ER-positive, HER2-negative breast cancer from three large clinical trials (ABCSG-6, ABCSG-8,

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Translational Relevance

Risk of recurrence has been traditionally evaluated using standard clinicopathologic factors, such as nodal status, tumor size, tumor grade, age, and IHC markers. Multigene assays are more frequently used to better determine prognosis and treatment options in women with hormone receptor–positive, HER2-negative breast cancer. Most of these multigene assays have been developed in women with invasive ductal carcinoma or of unknown histologic subtypes. Women with invasive lobular carcinoma have specific disease characteristics and outcomes vary by histologic subtypes. It is important to understand whether these multigene assays perform equally well in both subtypes and it is therefore necessary to evaluate the prognostic performance in this specific subtype.

TransATAC) were included in this analysis. All received 5 years of endocrine treatment as the only adjuvant therapy. The ABCSG-6 trial (ClinicalTrials.gov Identifier: NCT00309491) and ABCSG-8 trial (ClinicalTrials.gov Identifier: NCT0029175) included postmenopausal women with hormone receptor–positive breast cancer who received five years of tamoxifen alone or five years of tamoxifen plus aminoglutethimide for the first 2 years (15), or 5 years of tamoxifen or 2 years of anastrozole followed by 3 years of tamoxifen (16), respectively. Women in the TransATAC trial (ClinicalTrials.gov Identifier: NCT00849030) were postmenopausal and received 5 years of tamoxifen or anastrozole alone (17). Institutional review boards approved the individual studies, which were done in accordance with the Declaration of Helsinki (1996 revision). All women included in this analysis gave written informed consent.

The EndoPredict (EPclin) was developed in pre- and postmenopausal women with ER-positive, HER2-negative breast cancer (10). For the TransATAC cohort, EP molecular scores were generated by qRT-PCR gene analysis by Myriad Genetics, Inc. For ABCSG-6 and -8 cohorts, EP molecular analysis was carried out by the ABCSG research group. All parties were blinded to clinical outcome data. As described previously (14), the EP molecular score incorporates the expression of eight cancer-related genes (*BIRC5, UBE2C, DHCR7, RBBP8, IL6ST, AZGP1, MGP*, and *STC2*), three housekeeping genes (*CALM2, OAZ1*, and *RPL37A*), and one control gene (*HBB*). The EPclin incorporates information on nodal status and tumor size and higher EPclin scores indicate a higher risk of distant recurrence. Patients with an EPclin score of less than 3.3 are considered low risk, whereas those with an EPclin of higher or equal to 3.3 are high risk (10). We used the Clinical Treatment Score (CTS; ref. 18) to assess the additional prognostic value of EPclin to clinical parameters. In brief, the CTS contains information on nodal status, tumor size, grade, age, and treatment (tamoxifen vs. anastrozole).

Central review of lobular morphology was done in TransATAC (including subspecification of lobular subtypes) and ABCSG-6 (morphology and E-Cadherin testing). In ABCSG-8, no central review was performed. However, lobular breast cancers were defined either by morphology alone or in most cases in combination with E-cadherin testing by a pathologist. For this analysis, women with ILC or IDC histologic subtypes were included ($N = 2{,}414$). Rare subtypes, such as tubule-lobular, pleomorphic, and solid, were not the focus of this analysis ($N = 216$).

Statistical analysis

The primary endpoint was distant recurrence (DR), defined as the time from randomization in the primary study to DR of breast cancer. Local recurrence, regional recurrence, contralateral second primary, or secondary breast cancer in the ipsilateral breast were not considered as DR. Deaths due to breast cancer without DR occurring prior to death were also considered as a DR at the time of death. Other causes of deaths were not considered as an event. All analyses were censored at 10 years of follow-up.

The primary objective of this analysis was to determine the prognostic value of EPclin, alone or in combination with clinical parameters, for DR in women with ILC in the combined dataset. Secondary objectives included differential risk stratification by EPclin in women with ILC, subgroup analyses in patients with node-negative and node-positive ILC separately, prognostic value of EPclin for the risk of late DR in women with ILC, and comparison of prognostic value of EPclin between women with ILC versus IDC.

A predefined statistical analysis plan was approved by all research groups prior to data merge and data analyses. Ten-year distant recurrence risks were assessed using Cox proportional hazard models. To assess prognostic performance of EPclin and clinical parameters, partial likelihood ratio (LR χ^2) tests and HRs with associated 95% confidence intervals (CI) based on Cox proportional models were used. To compare the prognostic performance of EPclin and CTS, scores were normalized to have unit variance. The assumption of proportional hazards was assessed by Schoenfeld residuals. The improvement of DR in prognostication by EPclin compared with clinical and pathologic variables (CTS; ref. 18) was quantified by the increase in the LR χ^2 value (ΔLR χ^2; two-sided 5% significance level). Kaplan–Meier estimates were used to estimate mean 10-year DR risks in predefined risk groups. All statistical analyses were two-sided, and a P value of less than 0.05 was regarded as significant. All analyses were performed with Stata software (version 15.1; StataCorp).

Results

We had data for 2,630 postmenopausal women with ER-positive, HER2-negative breast cancer. Of these, 470 (19.5%) had ILC, 1,944 (80.5%) had IDC, and the remaining 216 (8.2%) had other histologic subtypes. Looking at the distribution of ILC by trial, 17.5% of women in ABCSG-6 had ILC, 20.7% in ABCSG-8, and 14% in TransATAC. Significantly more women in the ABCSG-8 trial had ILC compared with women in the TransATAC study ($P < 0.001$). **Table 1** shows baseline characteristics by histologic subtypes for the analysis cohort. In brief, women with ILC had significantly larger tumor size ($P < 0.001$), less differentiated tumors ($P < 0.001$), and higher CTS scores ($P < 0.001$) than women with IDC. Age, number of nodes involved, and EPclin scores were similar between the two subgroups (**Table 1**). For 22% of women with ILC, grade was not determined and therefore the CTS could not have been calculated. The median follow-up between the three trials was very similar and not significantly different: ABCSG-6: 9.02 years (IQR 5.0–11.5); ABCSG-8: 9.10 years (IQR 5.8–11.5); TransATAC: 9.9 years (IQR 7.7–10.1).

ILC

EPclin was highly prognostic in women with ILC [HR = 3.32 (2.54–4.34), $P < 0.0001$; **Table 2**]. EPclin provided significantly more prognostic value for DR in women with ILC than the CTS [ΔLR-χ^2 = 17.60 ($P < 0.0001$); **Table 2**]. 298 women (63.4%) were categorized as low risk by EPclin compared with 172 (36.6%) who were deemed high risk (**Fig. 1**). Women in the low EPclin risk group had a 10-year DR risk

Table 1. Baseline characteristics according to histological subtypes.

	ILC ($N = 470$)	IDC ($N = 1,944$)	P
Age (years), median (IQR)	63 (58–70)	64 (58–71)	0.40
Tumor stage			
T1a/b	49 (10.4%)	346 (17.8%)	
T1c	209 (44.5%)	1,020 (52.5%)	
T2	192 (40.9%)	559 (28.8%)	
T3	18 (3.8%)	18 (0.9%)	
Unknown	2 (0.4%)	1 (0.05%)	<0.001
Nodal status			
Negative	326 (69.4%)	1,360 (70.0%)	
1–3 positive	115 (24.5%)	490 (25.2%)	
4–10 positive	24 (5.1%)	78 (4.0%)	
10+ positive	5 (1.1%)	16 (0.8%)	0.69
Tumor grade			
Well	49 (10.4%)	482 (24.8%)	
Intermediate	301 (64.0%)	1,278 (65.7%)	
Poor	16 (3.4%)	180 (9.3%)	
Undetermined	104 (22.1%)	4 (0.2%)	<0.001
EPclin, median (IQR)	3.07 (2.51–3.55)	3.08 (2.56–3.73)	0.13
CTS, median (IQR)	120.2 (89.9–171.4)	102.0 (64.1–143.6)	<0.001

Note: For continuous variables the t-test was used and for categorical variables the χ^2 test was used to assess differences in baseline characteristics.

of 4.8% (2.7–8.4) compared with a 10-year DR risk of 26.6% (20.0–35.0) for women categorized into the high-risk group. This translates to an over six times higher risk of developing a DR for women in the high EPclin risk group compared to the low EPclin risk group [HR = 6.33 (3.31–12.12); $P < 0.0001$; **Fig. 1A**].

In women with node-negative disease, EPclin provided significant prognostic value for DR [HR = 2.56 (1.63–4.02), $P < 0.0001$], whereas CTS did not provide any significant prognostic value (**Table 2**). Almost 80% of women ($N = 260$) were categorized as low risk by EPclin with a 10-year DR risk of 4.6% (2.5–8.4; **Fig. 1B**). Those categorized into the high EPclin risk group [$N = 66$ (20.3%)], had a 4.4-fold increased risk in developing a DR [HR = 4.42 (1.84–10.65), $P = 0.001$] and a significantly higher 10-year DR risk [19.1% (10.6–33.3)] compared with those in the low-risk group. In women with node-positive disease ($N = 144$), 38 women (26.4%) were categorized as low risk by EPclin with the remaining women as high risk (73.6%). Significantly higher 10-year DR risks were observed for those in the EPclin high-risk group compared with those in the low-risk group [31.2% (22.4–42.3) vs. 6.4% (1.6–23.5); **Fig. 1C**]. In both nodal subgroups, EPclin provided significantly more prognostic information than the CTS alone (**Table 2**).

Table 2. Prognostic value of EPclin and CTS for women with ILC.

	HR (95% CI)	P	LR-χ^2	ΔLR-χ^2 (CTS + EPclin vs. CTS)
All				
EPclin ($N = 470$)	3.32 (2.54–4.34)	<0.0001	70.42	17.60 ($P < 0.0001$)
CTS ($N = 364$)	2.17 (1.73–2.72)	<0.0001	36.37	
Node-negative				
EPclin ($N = 326$)	2.56 (1.63–4.02)	<0.0001	13.65	8.52 ($P = 0.035$)
CTS ($N = 258$)	1.28 (0.62–2.64)	0.5	0.44	
Node-positive				
EPclin ($N = 144$)	3.70 (2.49–5.50)	<0.0001	35.71	9.07 ($P = 0.0026$)
CTS ($N = 106$)	2.12 (1.53–2.93)	<0.0001	18.96	
Years 5–10				
EPclin ($N = 397$)	3.83 (2.43–6.04)	<0.0001	32.43	21.38 ($P < 0.0001$)
CTS ($N = 313$)	1.66 (1.12–2.47)	0.012	5.33	

Note: Table shows prognostic value of EPclin according to patient population and time period. The LR test shows how strong a model is; the greater the value, the more prognostic value is provided.

EPclin was also highly prognostic for late DR in 397 women with ILC who were recurrence free 5 years after diagnosis [HR = 3.83 (2.43–6.04), $P < 0.0001$; **Table 2**]. Compared with the CTS alone, EPclin provided significantly more prognostic information for late DR [ΔLR-$\chi^2 = 21.38$ ($P < 0.0001$)], indicating a better prognostication for these late events. Two thirds of women were categorized to the low-risk group with a 5- to 10-year DR risk of only 2.4% (1.0–5.8) compared with 135 (34.0%) women categorized into the high EPclin risk group who had a 10-year risk of 16.1% (10.2–24.7).

We also investigated the molecular EP score as a prognostic marker and observed overall similar but weaker effect sizes than for the EPclin. In all women with ILC, molecular EP was highly prognostic [HR = 2.08 (1.65–2.64), $P < 0.0001$] and provided significant additional prognostic value to the CTS (ΔLR-$\chi^2 = 10.45$). For those with node-negative disease ($N = 326$), a 2.2-fold increase with every SD increase in molecular EP was observed [HR = 2.19 (1.56–3.08), $P < 0.0001$]. Similarly, in those with node-positive disease ($N = 144$) molecular EP was highly prognostic [HR = 2.31 (1.57–3.39), $P < 0.0001$] and provided additional prognostic value to the CTS (ΔLR-$\chi^2 = 5.64$).

Comparison between ILC and IDC

EPclin was highly prognostic in women with IDC ($N = 1,944$) overall [HR = 2.36 (2.11–2.65), $P < 0.0001$], and in all subgroups (**Fig. 2**). Overall, EPclin was more prognostic in ILC than IDC, with significant heterogeneity between the two subtypes ($P = 0.045$). For subgroups, wider CIs were observed due to fewer women with ILC and fewer DR events compared with women with IDC, and no significant heterogeneity was observed. EPclin categorized nonsignificantly more women with ILC (63.4%) as low risk compared with those with IDC (59.1%). Ten-year DR risks for low- and high-risk groups by EPclin were similar for those with ILC versus IDC (low risk: 4.8% vs. 5.4% and high risk: 26.6% vs. 23.5%, respectively).

Although special subtypes were not the focus of this analysis, EPclin was highly prognostic for DR in this subgroup of patients [$N = 216$; HR = 2.41 (1.74–3.35), $P < 0.0001$]. Numbers of DR in nodal subgroups were too small to make a meaningful interpretation (data not shown).

Discussion

This combined analysis of ABCSG-6, ABCSG-8, and TransATAC comprises the biomarker cohorts from three similar prospective phase III randomized trials that included postmenopausal patients with ER-positive, HER2-negative early breast cancer. All of these patients were treated with endocrine therapy (anastrozole, tamoxifen alone, or sequentially) after completion of local therapy and in the absence of chemotherapy. This retrospective analysis of prospectively recorded long-term follow-up data includes a total of 2,630 patients, of which 470 women had been diagnosed with a lobular breast cancer subtype. This cohort provides the opportunity to apply the validated gene expression signature EPclin to the largest, to our knowledge, lobular breast cancer cohort from phase III randomized trials.

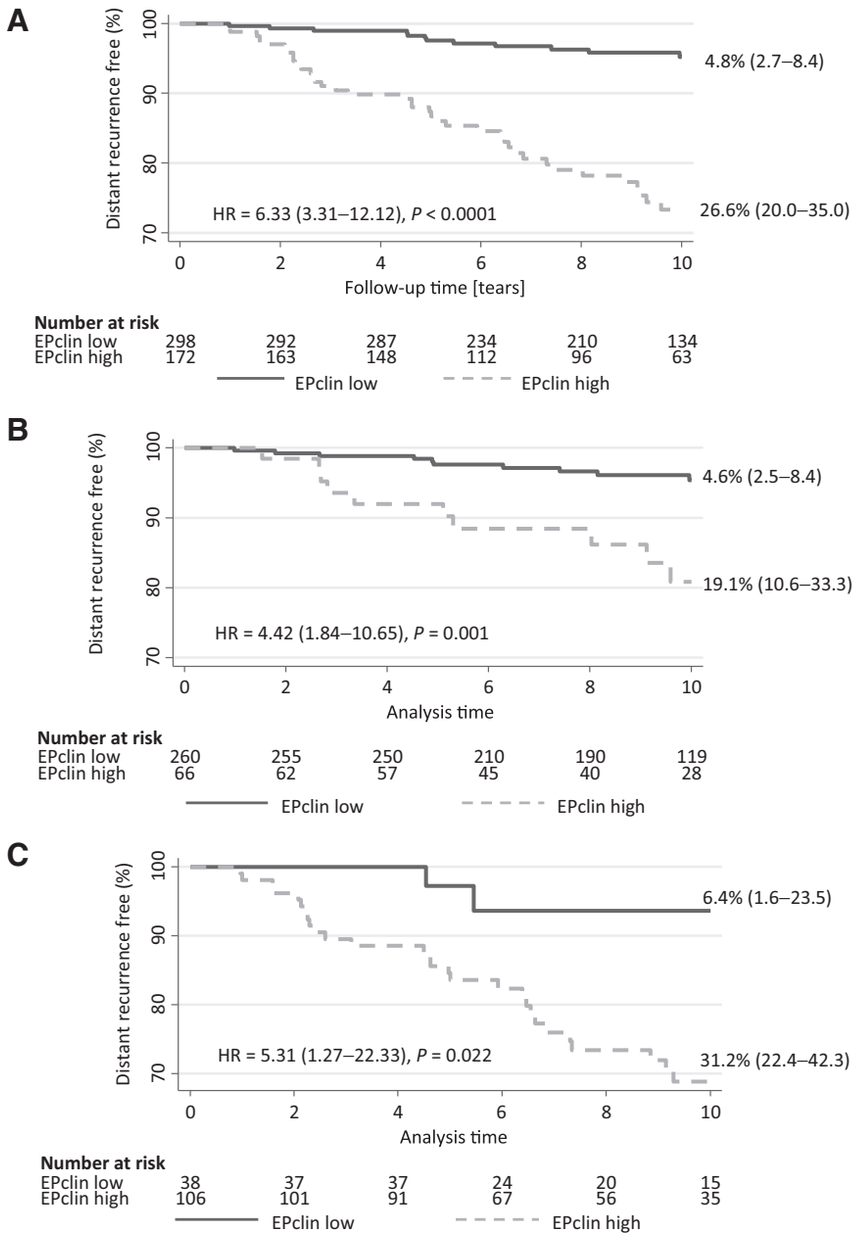

Figure 1.
Kaplan–Meier graphs and distant recurrence risks (%) according to EPclin risk groups for all women with ILC (**A**), node-negative ILC (**B**), and node-positive ILC (**C**).

Our results show that in this cohort of mostly low- to intermediate-risk patients, EPclin categorized almost two thirds (63%) of ILC cases into low risk, with 10-year DR risks of 4.8%. These results suggest a very favorable outcome, especially in comparison with women in the high-risk category, which had a 10-year DR risk of 26.6%. This subgroup of high-risk patients, which compromises 30% of all women with ILC, creates a strong rational for further studies to evaluate chemopredictive ability by EndoPredict. The absolute risk difference between low- and high-risk patients with ILC was 21.8%. The prognostic value of the test was similar for patients with and without lymph node metastasis and for late recurrences (late distant metastasis after 5 years of follow-up). Importantly, our results showed that in all subgroups and for early and late DR, EPclin provided substantially more prognostic information for ILCs than clinico-pathological parameters as captured by the CTS alone.

In the prognostic comparison of EPclin between lobular and ductal breast cancer no significant differences were observed, but numerically a higher relative number of lobular breast cancers seemed to be categorized into the low-risk group and the average 10-year risk of distant recurrence appeared higher for lobular cancers in the molecular high-risk group. The performance was surprisingly similar in ILC compared with IDC cancer despite clinical evidence attesting to biologic differences between the subtypes. Several lines of clinical evidence suggest that the term lobular breast cancer encompasses a distinct clinical entity. Lobular morphology is associated with distinct radiologic features such as multifocality and extensive intraductal components, distinct pathologic features such as growth in sheets, and lack of E-cadherin expression (19). The propensity for low-volume lymph node involvement is a particular challenge for clinical decision-making (20). Reports suggest that there is a 24% discordance in cases of low-volume nodal metastasis (21) and

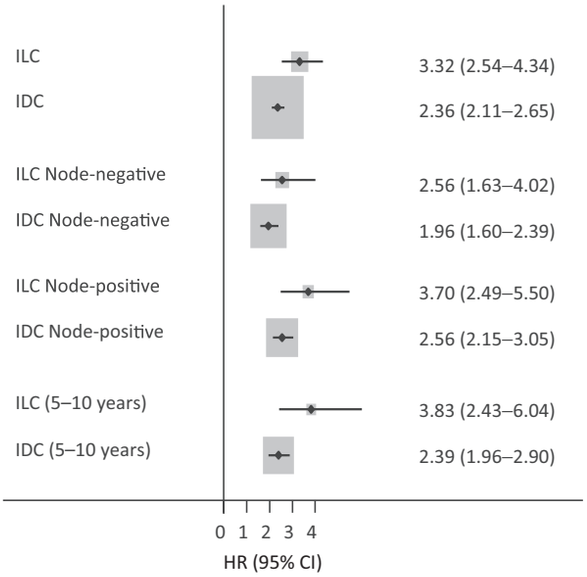

Figure 2.
Forest plot showing HRs with associated 95% CIs for ILC and IDC for overall population and subgroups.

better definitions in guidelines need to be defined. Moreover, response to neoadjuvant chemotherapy is poor in women with ILC (pCR 4.2% in hormone receptor–positive breast cancer; ref. 22). In terms of local therapy, these features and diffuse nature of ILCs lead to higher rates of second surgeries and higher mastectomy rates (23).

Genomic characterization shows two thirds of cases with lobular morphology harboring mutations in *CDH1* and half of lobular cases with alterations in *PIK3CA, PTEN* and *AKT1* (24). Activation of the HER pathway, via HER2 and HER3 mutations, show higher frequency in lobular as compared with ductal IBC. The genomic alterations found in lobular breast cancer are often quantitatively, but in several instances, qualitatively distinct from invasive ductal morphologies (25). Therefore, the successful validation of EPclin in this subtype was an important but not entirely expected finding. It is tempting to speculate that a gene expression test that comprises anatomical information, proliferation, and ER signaling/differentiation genes may be sufficient to improve the prognostication of patients with ILC. For truly predictive information concerning benefit from systemic adjuvant therapies, a detailed and reliable detection of DNA alterations may be necessary.

Our study has strengths and limitations. Strengths include the inclusion of a large cohort of well-characterized women with histologically confirmed ILC. Furthermore, we have clinical outcome data for all patients and used well-characterized tissue samples. EPclin for all trials was measured in the same laboratory, with all personnel being blinded to clinical outcome data. Limitations include small subgroups of patients with node-positive disease and a proportion of women with ILC for whom local grading was not determined. In this analysis, we were unable to determine the chemopredictive value of EPclin in women with ILC. Our results are only applicable for women who have received endocrine therapy only and cannot be extrapolated to those who have received chemotherapy.

In summary, EPclin showed excellent prognostic performance in ILC, for both lymph node–negative and lymph node–positive disease and for both early and late time points of distant recurrence. For the clinician, the added information of EPclin in this subset of patients may be of particular value: lobular breast cancer can often reach large total tumor diameters due to the sheet-like pattern of growth. Nodal metastasis can be frequent and of low volume, and the typical anatomic information may therefore appear less reliable. In addition, the described poor tumor shrinkage from neoadjuvant chemotherapy make clinical decisions concerning adjuvant cytotoxic treatment daunting at times. In this respect, EPclin is of added prognostic value above and beyond clinicopathologic assessment in both IDC and ILC, and may help patients to make better informed decisions concerning adjuvant cytotoxic and/or extended endocrine treatment.

Disclosure of Potential Conflicts of Interest

I. Sestak reports personal fees from Myriad Genetics, Nanostring Technologies, and Pfizer Oncology outside the submitted work. M. Filipits reports personal fees from AstraZeneca, Biomedica, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Myriad Genetics, Pfizer, and Roche outside the submitted work. M. Knauer reports grants from Agendia BV (unrelated research grant regarding Swiss SAKK study) outside the submitted work. R. Kronenwett reports other from Myriad Genetics (employee and previous shareholder with milestone payments) during the conduct of the study; in addition, Dr. Kronenwett is listed as a co-inventor on a patent owned by Myriad that relates to methods, kits and systems for the prognosis of the disease outcome of breast cancer, said method comprising : (a) determining in a tumor sample from said patient the RNA expression levels of at least 2 of the following 9 genes: UBE2C, BIRC5, RACGAP1, DHCR7, STC2, AZGP1, RBBP8, IL6ST, and MGP, (b) mathematically combining expression level values for the genes of the said set which values were determined in the tumor sample to yield a combined score, wherein said combined score is indicative of a prognosis of said patient; and kits and systems for performing said method. F. Fitzal reports personal fees from Roche, Novartis, and Pfizer (advisory board) outside the submitted work. J. Cuzick reports grants from AstraZeneca (research support for the institution) during the conduct of the study. M. Gnant reports grants and personal fees from AstraZeneca, Roche, and Novartis; grants and non-financial support from Pfizer; personal fees from Amgen, Celgene, Eli Lilly, Invectys; personal fees and non-financial support from Nanostring, and Medison outside the submitted work; and outside the submitted work, an immediate family member is employed by Sandoz. M. Dowsett reports grants from NIHR BRC during the conduct of the study; personal fees from Nanostring and Myriad (lecture fee) outside the submitted work. P. Dubskey reports grants from Myriad (research support via ABCSG) and other from Myriad (advisory via Hirslanden Klini St. Anna) during the conduct of the study; and grants Cepheid/Danaher, Agendia (research support via ABCSG), AstraZeneca, and Merck (advisory via Hirslanden Klinik St. Anna) outside the submitted work. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

I. Sestak: Conceptualization, resources, formal analysis, supervision, investigation, methodology, writing-original draft, project administration, writing-review and editing. **M. Filipits:** Investigation, writing-review and editing. **R. Buus:** Investigation, writing-review and editing. **M. Rudas:** Investigation, writing-review and editing. **M. Balic:** Investigation, writing-review and editing. **M. Knauer:** Investigation, writing-review and editing. **R. Kronenwett:** Data curation, investigation, writing-review and editing. **F. Fitzal:** Investigation, writing-review and editing. **J. Cuzick:** Conceptualization, resources, investigation, writing-review and editing. **M. Gnant:** Investigation, writing-review and editing. **R. Greil:** Investigation, writing-review and editing. **M. Dowsett:** Conceptualization, resources, data curation, investigation, methodology, writing-original draft, writing-review and editing. **P. Dubsky:** Conceptualization, resources, data curation, investigation, methodology, writing-original draft, writing-review and editing.

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