5 Minute JournalClub

POST-SABCS Issue 3, 2013

The EndoPredict® Score Identifies Late Distant Metastases in ER-Positive, HER2-Negative Breast Cancer

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual San Antonio Breast Cancer Symposium (SABCS) is unmatched in its significance with regard to the advancement of breast cancer treatment. This unique conference provides many clinicians and scientists from around the world a forum for discussing critical issues in the prevention and management of breast cancer. Therefore, SABCS is targeted by many members of the clinical research community as the optimal time to unveil new clinical data. This creates an environment in which yearly published results from a plethora of ongoing clinical trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all breast cancer subtypes.

Although SABCS currently offers online access to the vast majority of the poster and plenary presentations from the annual meeting, the absence of expert assessment concerning practical applications may yield confusion among community oncologists who are challenged almost daily to appropriately apply a multitude of scientific findings across diverse tumors. Thus, identification of those data sets with immediate or impending relevance to the delivery of quality breast cancer care, in conjunction with professional commentary to address resultant practice ambiguity, may prove vastly beneficial to those physicians who are unable to make the annual pilgrimage to San Antonio. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest SABCS, including expert perspectives on how these new evidence-based concepts can and should be incorporated into on- and off-protocol patient care. This activity will assist medical oncologists, radiation oncologists, breast/general surgeons, nurses and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Evaluate the EndoPredict® signature together with a predefined combination of clinicopathologic factors and molecular data as a predictor of late metastases for patients with estrogen receptor-positive and HER2-negative breast cancer.
- Assess the utility of the Onco*type* DX® Recurrence Score® in predicting benefit from the addition of paclitaxel to adjuvant doxorubicin/cyclophosphamide for patients with lymph node-negative and estrogen receptor-positive breast cancer treated concurrently with endocrine therapy.
- Compare the performance of the Breast Cancer Index℠ biomarker to that of the Onco*type* DX Recurrence Score and IHC4 score as prognostic factors for distant recurrence of hormone receptor-positive, lymph node-negative primary breast cancer.
- Determine the impact of metabolic syndrome on breast cancer recurrence for patients with high-, intermediate- or low-risk disease as defined by the 21-gene Onco*type* DX Recurrence Score assay.
- Appraise the reproducibility of IHC-based Ki-67 biomarker assays and ongoing strategies to increase concordance in analysis and scoring methods.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Advisory Committee, Consulting Agreements and Speakers Bureau: Amgen Inc, Bristol-Myers Squibb Company, Genentech BioOncology, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi; Research Support: Genentech BioOncology, GlaxoSmithKline, Sanofi.

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Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: April 2013
Expiration date: April 2014

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POST-SABCS Issue 3, 2013

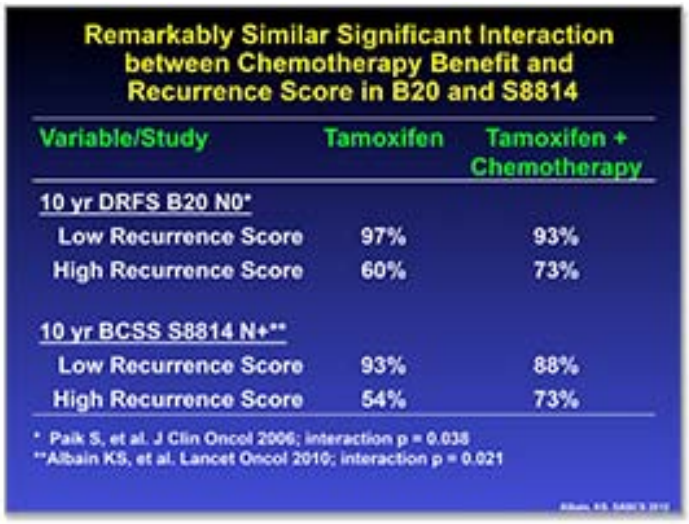
Adjuvant chemotherapy for patients with node-positive luminal A breast cancer

To go directly to slides and commentary for this issue, **click here**.

The December San Antonio Breast Cancer Symposium (SABCS) once again featured a bounty of papers focused on tissue predictors of response to systemic agents, and although none will shake up clinical practice like Dr Soon Paik's legendary 2004 SABCS presentation documenting the predictive value of the 21-gene Recurrence Score® (RS) in tumor samples from patients on the NSABP-B-20 trial of tamoxifen alone or with chemotherapy (CT), on a macro level these translational and clinical findings contribute significantly to our knowledge base and help further divide this disease into specific biologic subsets. However, other than being an outlet for new research data, SABCS is also an exceptional educational event where fascinating sessions often provide new perspectives on patient care.

To that end, the spectacular clinical science symposium on the first day of the conference included a thoughtful and thought-provoking overview by Dr Kathy Albain on the critical and controversial issue of adjuvant treatment for patients with the common luminal A phenotype, defined by Dr Charles Perou and others as having high ER and normal HER2 levels and relatively low proliferation. Dr Albain noted that last year's international meta-analysis demonstrated an overall benefit of CT in ER+ tumors, but the emergence of contemporary assays like the RS has now identified patients with ER+ tumors who are less likely to benefit from CT.

A critical issue in this regard is the patient with a node+ tumor, and to explore this Dr Albain took a unique tack by directly comparing the results of her work (presented in SABCS 2010) evaluating the RS in available tissue from the SWOG-8814 node+ study to the findings from Paik's initial evaluation of the assay in node-negative tumors from B-20. Interestingly, there was a remarkably similar correlation between CT benefit and RS in B-20 and S8814. However, more than 2 years later



controversy still surrounds the issue. Dr Albain referred to a 2012 ***JCO* editorial** by Dr Dan Hayes in which he enthusiastically supported enrolling eligible patients on the ongoing RxPONDER node+ trial but vehemently objected to withholding CT (and the potential to improve the chance of remaining disease free) in such individuals outside a study setting. As is often the case with education sessions of this type, Dr Albain did not provide a definitive recommendation about the use of tissue predictors in node+ disease, but at **our CME symposium that evening** a number of the faculty members, including Drs Hal Burstein, Kim Blackwell, George Sledge and Cliff Hudis, noted that they will selectively obtain a RS in patients with node+, ER+, HER2-negative tumors and a low nodal burden.

After hearing Dr Albain's talk, I invited her to participate in an audio interview, during which she was particularly enthused about the next generation of prospective trials, including TAILORx and RxPONDER (RS in node-negative and node+ settings) and MINDACT and I-SPY 1 (70-gene signature in the adjuvant and neoadjuvant settings), which have the potential to drastically shift how predictive assays are employed in clinical practice. However, until these trials begin to report, oncologists must make these difficult decisions with a less than optimal evidence base and keep abreast of incremental steps forward. In that regard, here's the bottom line on the most recent crop of related SABCS data sets.

1. More on RS in node+ tumors

A prominent SABCS paper focused on another retrospective/prospective analysis of tissue in patients with ER+ tumors in a large Phase III trial (NSABP-B-28, evaluating AC alone or with paclitaxel in patients with node+ disease) and provided additional evidence that RS can predict outcome in this population. Interestingly, the incremental gain from paclitaxel was not correlated with RS, but the analysis was underpowered to make that determination.

2. Molecular profiles to predict risk of delayed recurrence (DR) in patients completing 5 years of adjuvant endocrine treatment

The SABCS presentation of the ATLAS trial of 5 versus 10 years of tamoxifen was yet another data set demonstrating the critical role of DR in ER+ tumors, and 2 early but encouraging papers reported on novel RT-PCR assays to identify patients at particular risk for these events. The first looked at the **"EndoPredict® Score"** in tissue from 2 major Austrian trials, and the second examined the **"Breast Cancer Index"** versus RS and IHC4 in 665 primary tumor samples from the TransATAC tissue bank. Although not definitive, it appears that these or other similar assays may one day be able to provide important input on the critical clinical decision of extending endocrine treatment to 10 years or more while also yielding clues about specific genes correlated with the almost mysterious syndrome of DR, particularly in luminal A tumors.

3. Another dagger in the heart of Ki-67

Show this abstract to your friendly local pathologist the next time he or she offers a home brew that can save you the cost of a RS. After reviewing these scary numbers on lack of Ki-67 reproducibility among pathologists, unless perhaps Dr Mitch Dowsett or Dr Matt Ellis is doing your assay, you may want to rethink this approach.

4. Correlation between metabolic syndrome (MS) and breast cancer recurrence in luminal A tumors

This fascinating effort from Dr Albain's group attempted to determine whether the presence of MS is predictive of breast cancer recurrence in RS subtypes. In addition to documenting an overall eye-popping 27% rate of MS (glucose intolerance/diabetes and 2 other factors, including hypertension, dyslipidemia, central obesity and microalbuminemia) among the 332 patients in the study, of great interest was the correlation of MS and recurrence rate in patients with low RS. This intriguing finding suggests that the work of Dr Rowan Chlebowski and many others demonstrating a link between recurrence and metabolic factors like diet, obesity and exercise may be particularly relevant in luminal A tumors.

Next on this series: SABCS papers on CT, including a surprising potentially practice-changing paper on "pseudoadjuvant" treatment for patients with resected local recurrences rendered Stage IV with no evidence of disease.

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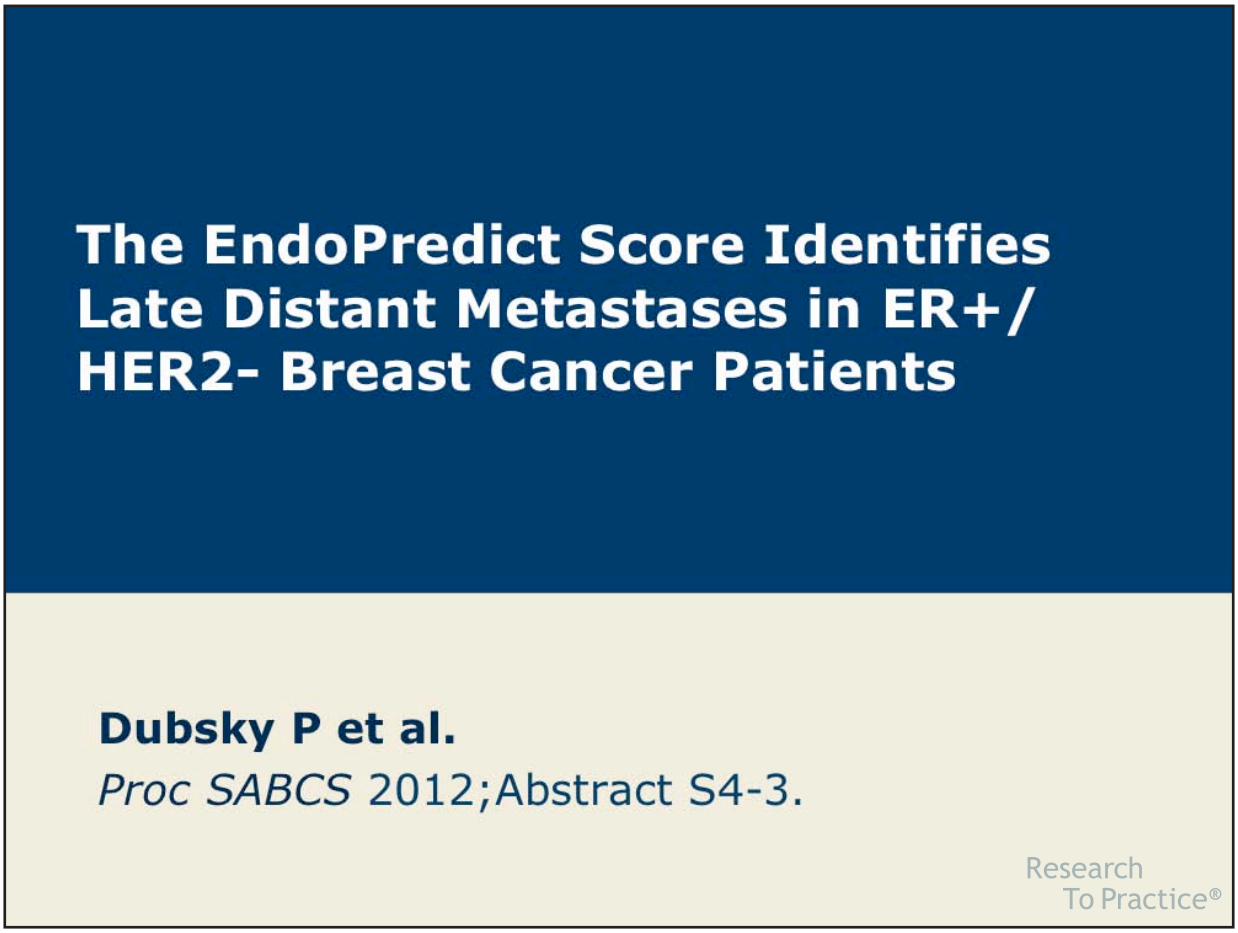
The EndoPredict Score Identifies Late Distant Metastases in ER-Positive, HER2-Negative Breast Cancer

Presentation discussed in this issue

Dubsky P et al. **The EndoPredict score identifies late distant metastases in ER+/ HER2- breast cancer patients.** San Antonio Breast Cancer Symposium 2012;**Abstract S4-3**.

Slides from a presentation at SABCS 2012 and transcribed comments from a recent interview with Lisa A Carey, MD (1/17/13)



Background

- In contrast to ER-negative breast cancer (BC), annual recurrence rates persist beyond 5 years for ER-positive disease, and the risk of BC-specific mortality is higher after 5 to 10 years of follow-up (*J Clin Endocrin Metab* 2012;97:e2201).
- Several ongoing trials are evaluating the benefit of extended aromatase inhibitor (AI) therapy and have identified factors, such as nodal positivity, tumor size, premenopausal status and ER/PR status, as useful elements for predicting benefit from extended AI therapy.
- Currently available multigene signatures have been trained to predict early recurrences but commonly fail to predict late events (*Breast Cancer Res Treat* 2011;129:607).
- **Current study objective**: To evaluate whether the EndoPredict® (EP) signature can identify late metastases in patients with ER-positive/HER2-negative BC, and to determine if a predefined combination of nodal status and tumor size with molecular data (EPclin) could further improve this prediction.

Dubsky P et al. *Proc SABCS* 2012;Abstract S4-3.

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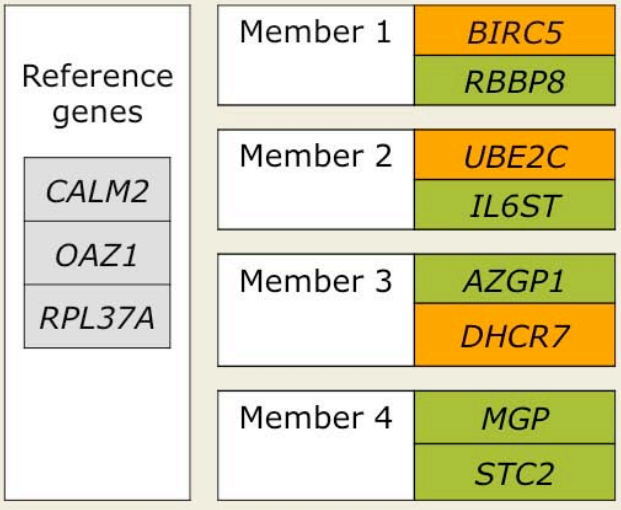
The EP and EPclin Signatures

- The EP signature contains 8 cancer-related genes and 3 reference genes (*Clin Cancer Res* 2011;17:6012).



- EP was determined using qRT-PCR and formalin-fixed, paraffin-embedded tissue samples.
- EP signature was trained on samples from tamoxifen (TAM)-treated women (n = 964).
- EP signature was validated using samples from patients on the Phase III ABCSG-6 (n = 378) and 8 (n = 1,324) trials.
- EPclin is a predefined score incorporating EP, tumor size and nodal status.

Dubsky P et al. *Proc SABCS* 2012;Abstract S4-3.

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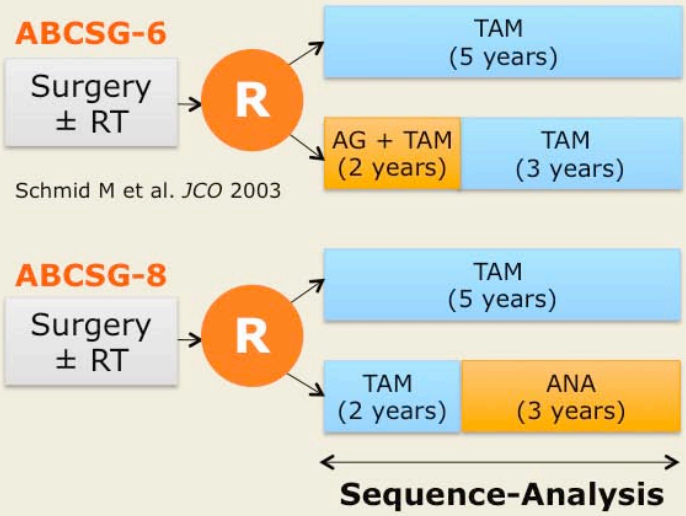
Patients and Methods



- 1,702 postmenopausal patients with ER-positive/ HER2-negative BC
- Two thirds of patients with tumor size less than 2 cm and N0
- No adjuvant chemotherapy
- 998 patients at risk after 5 y (median follow-up = 7.12 y)
- Primary endpoint was distant metastasis-free survival

TAM = tamoxifen; AG = aminoglutethimide; ANA = anastrozole

Dubsky P et al. *Proc SABCS* 2012;Abstract S4-3.

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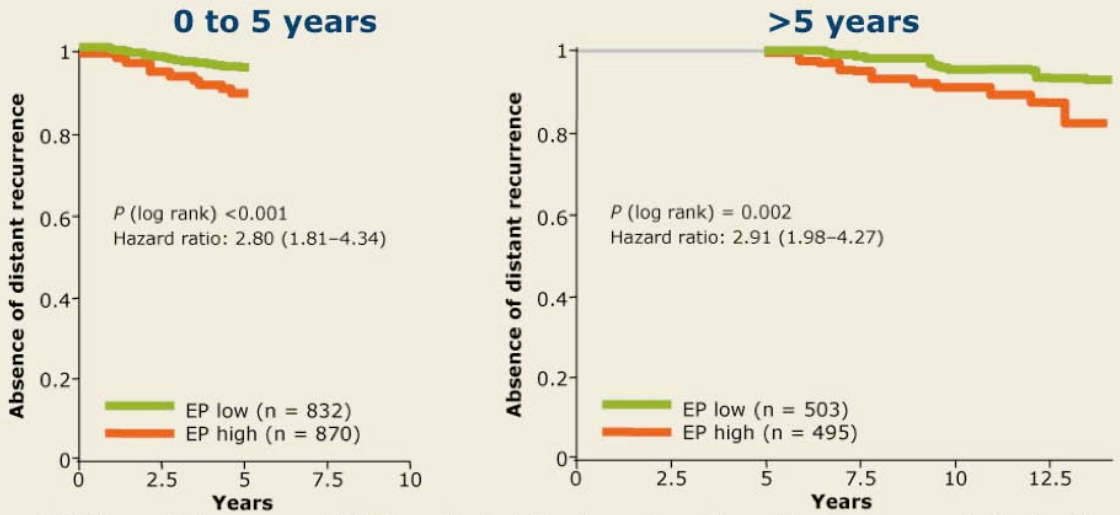
Distant Metastasis-Free Survival (DMFS)



- EP low-risk group (49% of pts) had a significantly improved clinical outcome before and after 5 y of follow-up:
  - 96.3% were distant metastasis free between 5 and 10 y

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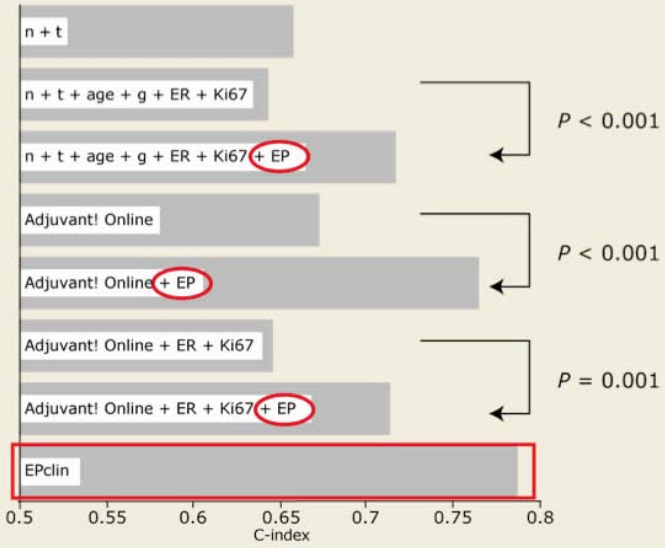
Prognostic Performance After 5 Years

C-index* (>5 years)



- The EndoPredict Score improves the prognostic performance of all common clinical parameters.
- The EPclin — a predefined score of EndoPredict and the clinical parameters nodal status and tumor size — showed the best performance to predict late metastases.

* C-index = measure of prognostic performance

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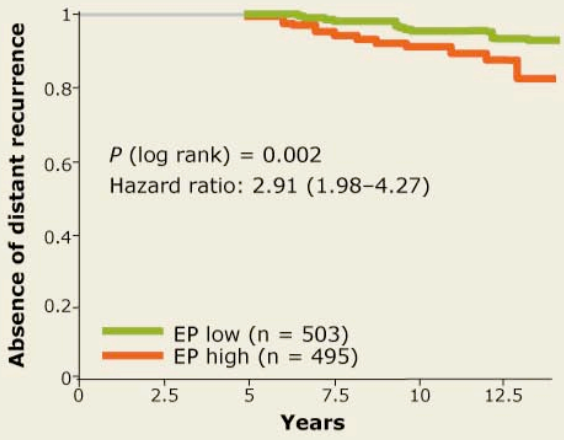
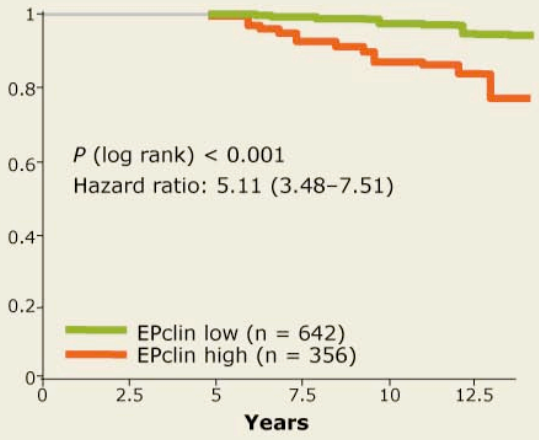
EP Score versus EPclin Score

EP low risk (49% of pts) >5 y



96.3% pts were distant metastasis free at 5-10 y

EPclin low risk (64% of pts) >5 y



>98% pts were distant metastasis free at >5 y

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Prognostic Contribution of ER Signaling and Cell Proliferation Genes

Variable	0-5 years Unit HR (95% CI)	*p*-value	>5 years Unit HR (95% CI)	*p*-value
Proliferation	1.60 (1.33-1.92)	<0.001	1.19 (0.85-1.67)	0.297
ER signaling	0.89 (0.75-1.06)	0.204	0.61 (0.46-0.81)	<0.001
Age	1.03 (1.00-1.06)	0.039	0.98 (0.93-1.02)	0.355
Nodal status	2.20 (1.71-2.83)	<0.001	2.50 (1.60-3.90)	<0.001
Tumor size	1.26 (0.94-1.70)	0.123	1.15 (0.69-1.93)	0.585
Ki67	1.00 (0.98-1.03)	0.727	1.01 (0.97-1.06)	0.502
Grade	1.23 (0.78-1.93)	0.364	0.69 (0.35-1.36)	0.285
Treatment arm	0.92 (0.59-1.43)	0.712	0.89 (0.39-2.05)	0.783

- Proliferation genes add independent prognostic information for early recurrence.
- Genes associated with ER signaling add independent prognostic information for late recurrence.

Dubsky P et al. *Proc SABCS* 2012;Abstract S4-3.

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Author Conclusions

- The EP score identifies early and late recurrences and offers independent prognostic information (data not shown) beyond what can be achieved with all common clinical parameters.
- Proliferation genes add prognostic information for identifying early recurrences, whereas genes associated with ER signaling are important for late events.
- The EPclin score identified a low-risk subgroup containing 64% of patients at risk after 5 years:
  - 98.2% of these women remain free of distant metastases 10 years after diagnosis.
- The risks and side effects of extended therapy should be weighed against this projected outcome.

Dubsky P et al. *Proc SABCS* 2012;Abstract S4-3.

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Investigator Commentary: EndoPredict Score and Identification of Late Distant Metastases in ER-Positive/HER2-Negative BC

EndoPredict (EP) is an 8-gene signature that was developed comprising proliferation and estrogen receptor signaling-related genes. A variation of the EP score, known as EPclin, takes into account the clinical variables of tumor size and nodal status. This group demonstrated that the EP score predicted both early and late relapses and performed better at predicting late relapses. They also performed an ontogenic-like exploration study of what drove the prognostic ability of the score, and the proliferation genes predicted early relapse, whereas the genes involved in estrogen receptor signaling predicted late relapse. To me, these results with the EP score were compelling. This group has examined a late relapse endpoint effectively.

There are now several of these prognostic genomic tests, such as the Onco*type* DX®, MammaPrint®, Breast Cancer Index℠ and PAM50, coming into clinical use, and we don't always know which test is better to use. I believe what we would like to have is a big, international, multiorganization, mature data set to analyze in order to perform an ubercomparison.

Interview with Lisa A Carey, MD, January 17, 2013