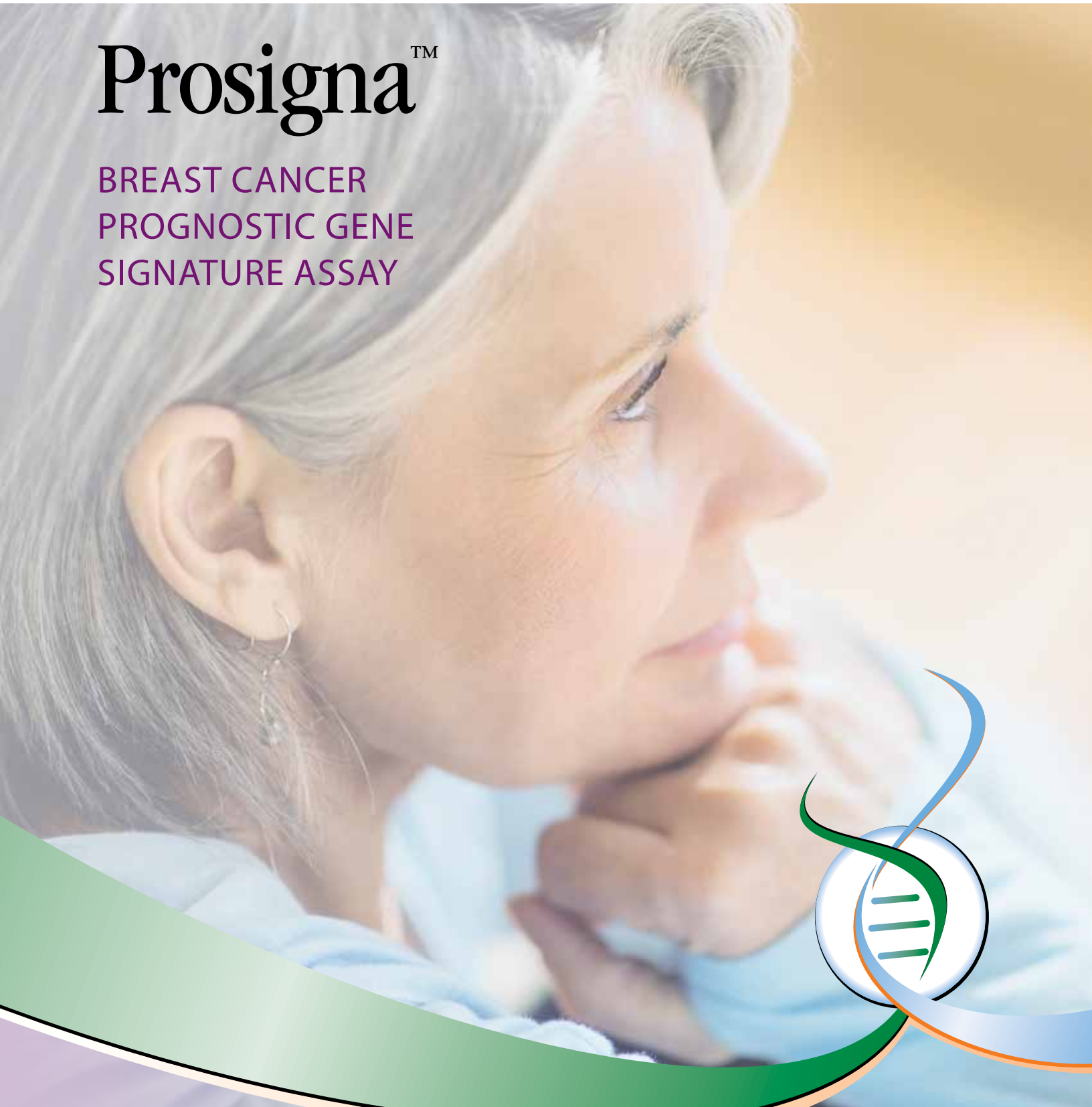
Integrated ONCOLOGY

LabCorp Specialty Testing Group

Prosigna™

BREAST CANCER PROGNOSTIC GENE SIGNATURE ASSAY



Methodology

The test is based on the reported 50-gene classifier algorithm originally named PAM50 and is performed on the nCounter® Dx Analysis System using RNA extracted from formalin-fixed paraffin-embedded (FFPE) tumor tissue samples. The nCounter-based platform uses gene-specific probe pairs that hybridize directly to the mRNA sample in a single tube reaction without amplification. Digital bar code technology then directly measures gene expression. This digital technology offers a high level of reproducibility, precision, and sensitivity.

Specimen Requirements

Formalin-fixed paraffin-embedded (FFPE) tumor tissue samples:

- Blocks – Preferred
- Up to six pre-cut unstained slides and one matching H&E-stained slide. 10 µm sections on positively charged slides.

The number of slides required is based on the measured tumor surface area. See chart below. Please note: Tumors with less than a 20 mm^2 surface area are less likely to meet the RNA input requirements.

Measured Tumor Surface Area on H&E Slide (mm^2)	Number of Unstained Slides
04-19	6
20-99	3
≥100	1

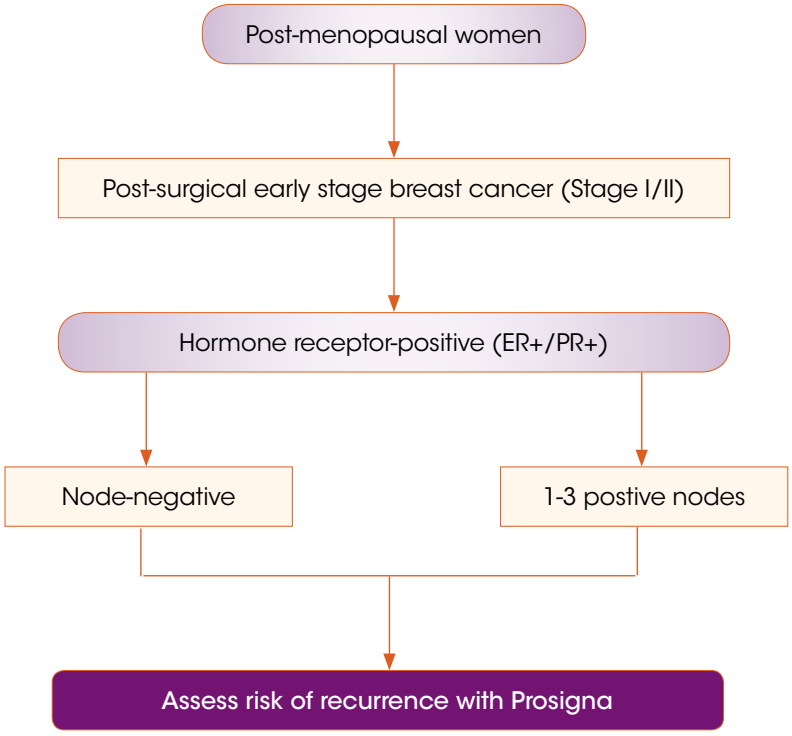
References

1. Package Insert: Prosigna Breast Cancer Prognostic Gene Signature Assay; Version 01, created 2013-09; REF LBL-C0223-01
2. Sestak, I et al., Factors Predicting Late Recurrence for Estrogen Receptor-Positive Breast Cancer. *J Natl Cancer Inst* 2013; 105:1504-11.
3. Dowsett, M et al., Comparison of PAM50 Risk of Recurrence Score With Oncotype DX and IHC4 for Predicting Risk of Distant Recurrence After Endocrine Therapy. *J Clin Oncol* 2013; 31:2783-90.
4. Jakesz, R et al., Tamoxifen and anastrozole as a sequencing strategy in postmenopausal women with hormone-responsive early breast cancer: updated data from the Austrian breast and colorectal cancer study group trial 8. *Cancer Res* 2009; 69:(2 Suppl):Abstract nr 14.
5. Dowsett, M et al., Prediction of Risk of Distant Recurrence Using the 21-Gene Recurrence Score in Node-Negative and Node-Positive Postmenopausal Patients With Breast Cancer Treated With Anastrozole or Tamoxifen: A TransATAC Study. *J Clin Oncol* 2010; 28:1829-1834
6. Gnant, M et al., Predicting risk for late metastasis: The PAM50 risk of recurrence (ROR) score after 5 years of endocrine therapy in postmenopausal women with HR+ early breast cancer. A study on 1,478 patients for the ABCSG-8 trial. *Ann Oncol* 2013; 24 (Supplement 3):iii29–iii37.

GENE EXPRESSION PROFILING WITH PROSIGNA™

What is Prosigna?

Prosigna™ Breast Cancer Prognostic Gene Signature Assay is an FDA-approved assay which provides a risk category (low, intermediate, high) and a numerical score (0-100) for the assessment of distant recurrence of disease at 10 years for post-menopausal women with early stage, hormone receptor-positive, invasive breast cancer.[1]



Indications

Per the FDA approval/package insert, the following are indications for use of Prosigna in female breast cancer patients who have undergone surgery in conjunction with locoregional treatment consistent with standard of care, either:

- A prognostic indicator for distant recurrence-free survival (DRFS) at 10 years in post-menopausal women with hormone receptor-positive, lymph node-negative, Stage I/II breast cancer to be treated with adjuvant endocrine therapy alone, when used in conjunction with other clinicopathological factors.[1]
- A prognostic indicator for DRFS at 10 years in post-menopausal women with hormone receptor-positive, lymph node-positive (1–3 nodes), Stage II breast cancer to be treated with adjuvant endocrine therapy alone, when used in conjunction with other clinicopathological factors. The assay is not intended for patients with 4 or more positive nodes.[1]

HEAD-TO-HEAD COMPARISON

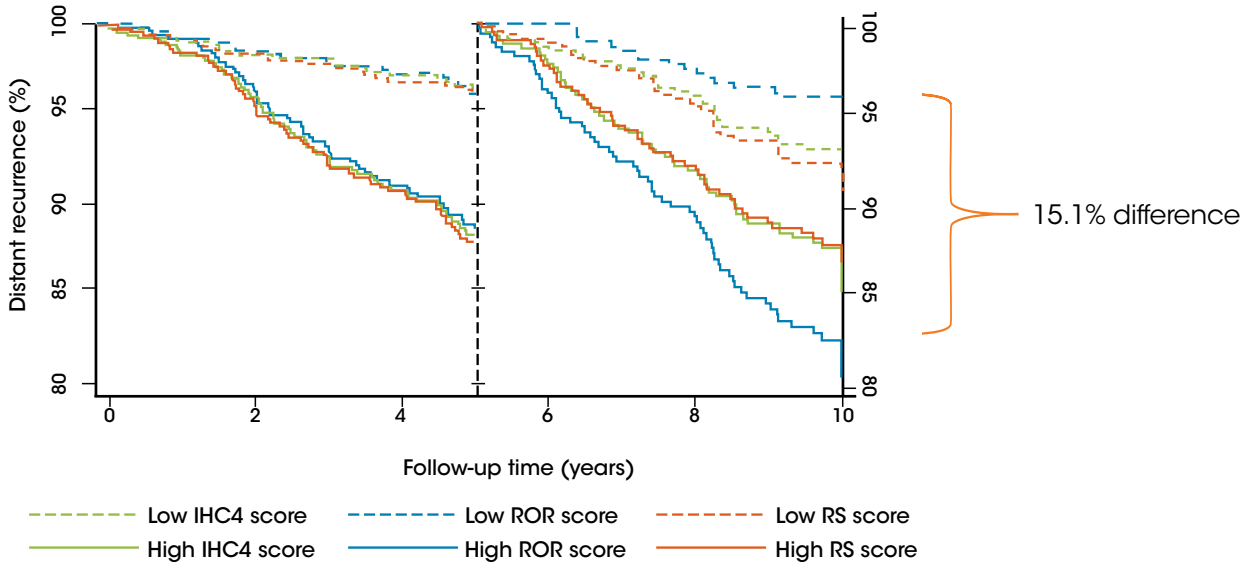
Comparison of Prosigna with Other Risk Recurrent Breast Cancer Assays

Prediction of Late Recurrence

A retrospective analysis of more than 1,000 patient samples from the TransATAC study evaluated the relationship between clinical variables, immunohistochemistry markers (IHC4), Oncotype DX® Recurrence Score (RS), and Prosigna Score (ROR) for distant recurrence in years 0-5 and years 5-10 in post-menopausal women with hormone receptor-positive breast cancer. Findings include:

- IHC4, RS, and ROR scores each added overall prognostic information beyond established clinicopathological factors in 0-5 year follow-up for distant recurrence.[2]
- However, IHC4 and RS lost most of their prognostic value after 5 years of follow-up.[2]
- Prosigna's ROR score showed the highest differential between patients in low-risk and high-risk groups in the 5-10 year follow-up period (15.1% difference), and was noted as the best discriminator between the two groups.[2]

Kaplan-Meier estimates for distant recurrence according to immunohistochemical markers (IHC4), recurrence score (RS), and risk of recurrence (ROR) score group split at the median value.[2]



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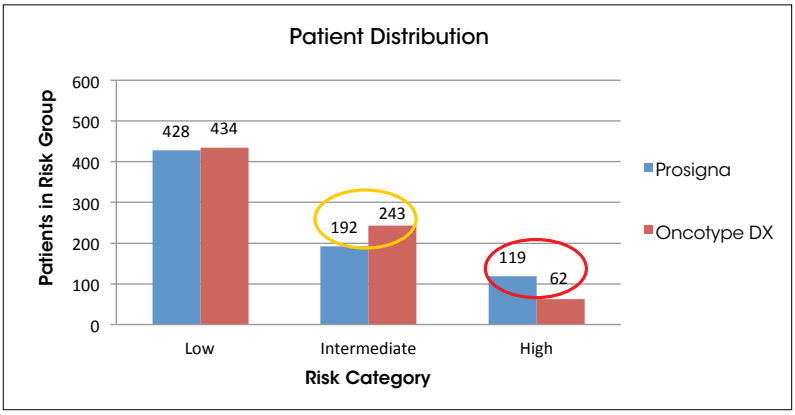
Fewer Intermediate Risk Scores

In assessing the patient distribution by risk categories in the TransATAC node-negative patient subset, the Prosigna assay was found to provide more prognostic information for the assessment of disease at 10 years, with fewer patients categorized as intermediate risk and more as high risk when compared to the Oncotype DX.[3]



Clinical-pathological variables excluded. N=739

VALIDATED CLINICAL PERFORMANCE

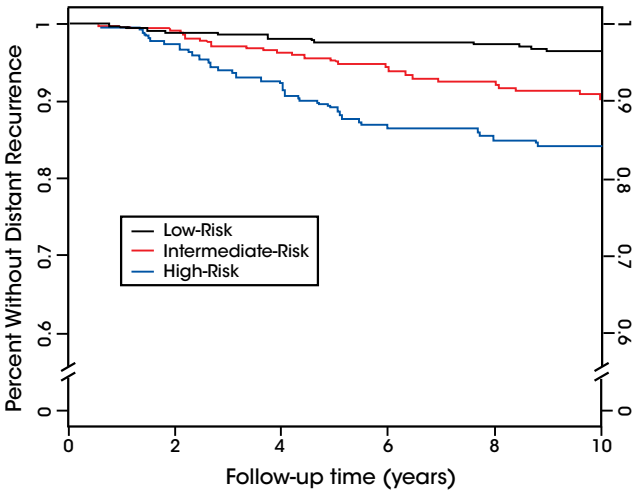
Prosigna Validated in Two Clinical Studies

Prosigna's clinical performance has been validated in two large independent studies using retrospective tissue samples from over 2,400 patients within the intended use population.*

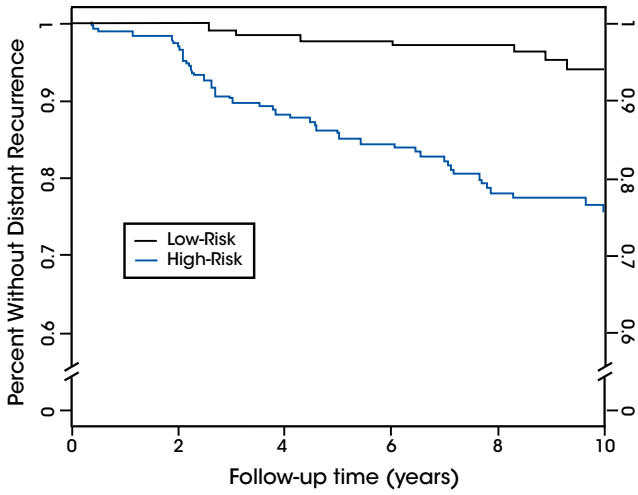
- Both the ATAC and ABCSG-8 trials assessed the benefit of adjuvant treatment (tamoxifen and anastrozole alone or in combinations for 5 years) in post-menopausal women with hormone receptor-positive early stage breast cancer.[1,4,5]
- A subset of tumor samples from the TransATAC (translational arm of the ATAC trial) and ABCSG-8 trials were analyzed by Prosigna to assess the assay's ability to predict risk of distant recurrence.[3,5,6]
- Both studies demonstrated that the Prosigna Score provided substantial prognostic information over and above the standard clinical variables (nodal status, tumor size and grade, age, and treatment) in predicting risk of distant recurrence.[1,3,6]

Kaplan-Meier curves and data tables showing the percent of patients without distant recurrence by risk group through 10 years and by node status[1]

DRFS by Risk Group for Node-Negative Patients



DRFS by Risk Group for Node-Positive (1-3)



Risk Group	Number of Patients (Percentage)	Number of Events Through 10 Years	Estimated Percentage Without Distant Recurrence at 10 Years (Range)
Low	487 (47%)	15	96.6% (94.4-97.9%)
Intermediate	335 (32%)	28	90.4% (86.3-93.3%)
High	225 (21%)	32	84.3% (78.4-88.6%)

Risk Group	Number of Patients (Percentage)	Number of Events Through 10 Years	Estimated Percentage Without Distant Recurrence at 10 Years (Range)
Low	158 (41%)	7	94.2% (88.1-97.2%)
High	224 (59%)	46	75.8% (68.9-81.4%)

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*post-menopausal women with hormone receptor-positive early stage breast cancer

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