Prosigna® breast cancer prognostic gene signature assay: Tailoring adjuvant treatment in early breast cancer

Tumor profiling using genomic assays such as Prosigna helps to personalize adjuvant treatment in patients with early breast cancer who would derive only little benefit from chemotherapy. At the 16th St. Gallen International Breast Cancer Conference, experts discussed the prognostic performance of the Prosigna assay in different risk groups as well as scientific comparisons between genomic assays.

Genomic assays have recently gained importance for the determination of patient prognosis in early breast cancer. Prosigna measures the expression of 50 genes to classify tumors in 4 different intrinsic subtypes (Luminal A, Luminal B, HER2-enriched and basal-like) that differ considerably with respect to their relapse patterns. Hormone-receptor (HR)-positive/HER2-negative breast cancer includes all subtypes, as does HER2-positive and HR-negative/HER2-negative disease.[1] "The intrinsic subtype classification based on IHC doesn't show to be an adequate surrogate for the genomic subtypes as determined by Prosigna" stressed Eva Ciruelos, MD, PhD, Medical Oncology Department, Hospital 12 de Octubre, Madrid, Spain.

Moving to precision medicine: Clinical utility of molecular subtypes in breast cancer

Prosigna is a CE marked and FDA 510(k) cleared genomic test for use in postmenopausal patients with HR-positive/HER2-negative early breast cancer to support adjuvant treatment decisions in both, node-negative and node-positive patients. The Prosigna report provides an individual risk of recurrence score (ROR) on a 0 to 100 scale which is correlated with the probability of distant recurrence (DR) at 10 years. Based on the genomic information together with clinical variables, including tumor size and nodal status, patients are classified into 3 risk categories (low, intermediate and high) that enables the identification of patients who might not benefit from the addition of chemotherapy.

Prosigna in the adjuvant setting

A combined analysis of the TransATAC and ABCSG-8 trials provided high-quality evidence for the clinical validity of Prosigna regarding prediction of 10-year DR risk in postmenopausal patients receiving adjuvant endocrine therapy alone.[3] In all tested subgroups, including positive lymph nodes, the ROR score and the intrinsic subtypes significantly added prognostic information to the clinical predictor. As Dr Ciruelos stated: "The Luminal A and Luminal B intrinsic subtypes were shown to have significantly different 10 years DR risk irrespective of nodal status".[2]

The results obtained by the study of the Danish Breast Cancer Group (DBCG) reinforce the data of Prosigna with real-world evidence. In a Danish cohort study of 2,558 postmenopausal women allocated to 5 years of endocrine therapy, the assay was shown to reliably identify patients who can be spared treatment with adjuvant chemotherapy irrespective of the number of affected lymph nodes.[2] The authors demonstrated a continuous relationship between the 10-year DR risk and the ROR score by number of positive nodes[2] (**Figure 1**).

Likewise, the probability of achieving pathological complete response following neoadjuvant chemotherapy correlates with the intrinsic subtype and thus with the ROR score.[4]

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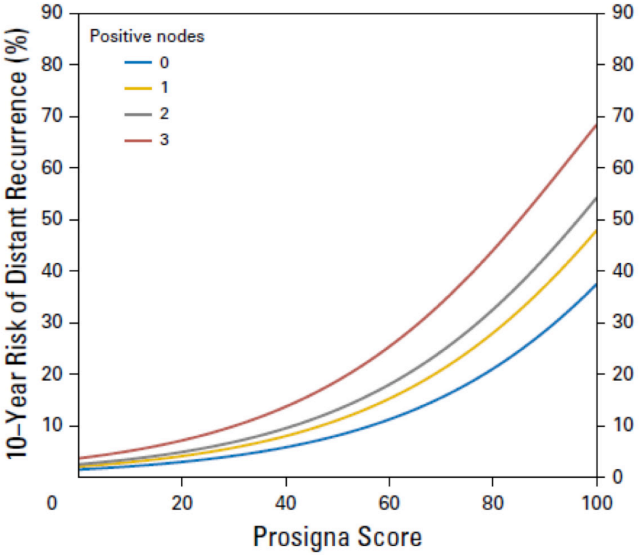

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Prosigna Breast Cancer Prognostic Gene Signature for use on nCounter Dx Analysis System is 510(k) cleared for *in vitro* diagnostic use in the United States. See package insert at www.prosigna.com for details. Note that intrinsic subtype is not reported by the Prosigna Assay in the United States.

Prosigna is being used as a stratification tool in the ongoing phase II CORALLEEN trial that is comparing neoadjuvant chemotherapy with letrozole plus ribociclib in Luminal B breast cancer. "Future prospective studies should establish the clinical utility of intrinsic subtypes in many different settings," Dr. Ciruelos said.

Prosigna real-world evidence and data in adjuvant DBCG trials

Bent Ejlertsen, MD, PhD, Copenhagen University Hospital, Denmark, referred to the DBCG 77B trial that compared cyclophosphamide, methotrexate and 5-fluorouracil (CMF) with oral cyclophosphamide, levamisole, and no adjuvant therapy in premenopausal patients with high-risk breast cancer.[5] "The findings obtained with Prosigna suggested that breast cancer patients with HER2-enriched and Luminal A subtypes derive little benefit from adjuvant cyclophosphamide-based chemotherapy regarding disease-free survival (DFS),[6]" Dr. Ejlertsen reported. At the same time, those with basal-like tumors experienced large effects, whereas patients with Luminal B disease had an intermediate benefit. According to a multivariate analysis, Prosigna's intrinsic subtypes predicted a benefit of cyclophosphamide-based chemotherapy for both DFS and OS. Prosigna pre-planned commercial cut-off points analysis for ER+/HER2- negative early breast cancer patients showed ROR≤40 no benefit from chemo and ROR>40 significant benefit from chemotherapy.

The NCIC.CTG MA.5 trial, identified favorable anthracycline benefit vs cyclophosphamide-based regimens primarily in the HER2-enriched subtype.[7] This study compared CMF vs CEF in node-positive premenopausal breast cancer patients. While patients with HER2-enriched tumors showed significantly improved relapse-free survival (RFS) and OS with CEF compared to CMF, there was no difference in those with basal-like tumors. "Data from the DBCG 89D trial support this finding[8]," Dr. Ejlertsen emphasized. "We confirmed a substantial benefit by substituting CMF with CEF in patients with HER2-enriched subtype."

UK NICE Diagnostic Guidance 2018 recommendation

Based on the 2000 NIH Consensus Conference on adjuvant therapy for breast cancer, adjuvant polychemotherapy was recommended for most patients with primary breast cancers larger than 1 cm regardless of nodal, menopausal, or hormone receptor status. Chemotherapy does induce relative risk reductions in the overall breast cancer population. "However, the absolute benefit is small in patients with a risk of recurrence of less than 10%[9]," noted Andreas Makris, MD, Mount Vernon Cancer Centre, UK. "This cutoff was used in the development of the genomic assays."

As Dr. Makris pointed out, Prosigna is recommended by many guidelines including the St. Gallen Guidelines 2017 update,[10] the NCCN Guidelines,[11] the ASCO 2017 Guidelines[12] and the ESMO Guidelines.[13] Also, the NICE diagnostics guidance DG34 for tumor profiling tests to guide adjuvant chemotherapy decisions in early breast cancer recommends Prosigna and other assays in ER+/HER2-, node-negative disease if an intermediate risk of DR has been demonstrated using a validated tool.[14] The tests should help decide whether to use adjuvant chemotherapy in a given patient. Importantly, patients with micrometastases are also included as eligible for testing. NICE did also run a specific evaluation comparing the prognostic performance of several genomic assays based on the 10-year DR rates by risk stratification. When looking particularly to N0 and intermediate risk (NPI>3.4) patients with Prosigna, Oncotype DX, IHC4+C and EPClin, the head-to-head comparison highlighted the accuracy of Prosigna. Patients assigned as low risk with Prosigna have the lowest risk of recurrence at 10-year (7.7%) compared to the other tests (14.6% and 15.2% might not benefit from the addition of chemotherapy for Oncotype DX and EPClin respectively) highlighting Prosigna accuracy in discriminating true low risk patients (**Table 1**).

Population LN0 NPI > 3.4	10-year distant metastasis-free interval (95% CI)			
	Oncotype DX	Prosigna	IHC4+C	EPClin
Low Risk	0.854 (0.776-0.907)	**0.923 (0.825-0.967)**	0.873 (0.787-0.926)	0.848 (0.761-0.905)
Intermediate Risk	0.798 (0.694-0.869)	0.796 (0.687-0.870)	0.788 (0.688-0.859)	N/A
High Risk	0.749 (0.598-0.851)	**0.699 (0.584-0.788)**	0.769 (0.645-0.855)	0.774 (0.688-0.838)

Table 1. 10-year distant recurrence rates by risk classification for Oncotype DX, Prosigna, IHC4+C and EPClin. Adapted from Table 124-Diagnostics Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence. (available online https://www.nice.org.uk/guidance/dg34/history)

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Direct comparison of signatures & prospective trials (OPTIMA and EXPERT)

Sestak *et al.* conducted an analysis directly comparing six prognostic signatures, including the Clinical Treatment Score (CTS), for DR (0-10 years) and late DR (5-10 years).[15] "In years 0 to 10 in the node-negative population, all the tests provided information in addition to clinico-pathological prognostic factors," Dr. Makris said. "But Prosigna provided the strongest prognostic information of all the tests." Extra information was also derived from all signatures in the node-positive cohort, although this effect was comparatively weaker. Nevertheless, even in this scenario, Prosigna added significant information beyond the clinical treatment score for N+ patients.

The ongoing, large-scale, prospective, non-inferiority OPTIMA trial (open in the UK and Norway) will provide level 1A evidence for the benefit of a decentralized test-guided chemotherapy decisions. Compared with other prospective trials of genomic assays (such as the recently published TailorX study), OPTIMA evaluates the utility of Prosigna in higher risk (primarily N1/N2) early breast cancer patients. This large study opened to recruitment in January 2017 and is expected to have a global impact on patient treatment. It will assess the clinical utility and cost-effectiveness of Prosigna, which was chosen based on economic modeling and the relative performance of six tests. To date, a total of 1,348 patients have been enrolled at 94 centers, towards a total aim of 4.500 patients.

Another ongoing study in Australia and New Zealand is the randomized, phase III, prospective EXPERT trial that uses Prosigna to guide the decision for adjuvant radiation therapy versus observation following breast-conserving surgery and endocrine therapy in patients with Luminal A early breast cancer.

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For more information visit www.prosigna.com or email info@prosigna.com

Source: 16th St. Gallen International Breast Cancer Conference 2019, satellite symposium sponsored by NanoString®, 22nd March, 2019, Vienna

1 Cejalvo JM *et al.*, Cancer Treat Rev 2018; 67: 63-70 ; 2 Lænkholm AV *et al.*, J Clin Oncol 2018; 36: 735-740 ; 3 Gnant M *et al.*, Ann Oncol 2014; 25(2): 339-345 ; 4 Prat A *et al.*, Clin Cancer Res 2016; 22(3): 560-566 ; 5 Ejlertsen B *et al.*, Cancer 2010; 116: 2081-2089 ; 6 Jensen MB *et al.*, Breast Cancer Res 2018; 20(1): 79 ; 7 Cheang MC *et al.*, Clin Cancer Res 2012; 18(8): 2402-2412 ; 8 Ejlertsen B *et al.*, Eur J Cancer 2007; 43: 877-884 ; 9 EBCTCG, Lancet 2005; 365(9472): 1687-1717 ; 10 Curigliano G *et al.*, Ann Oncol 2017; 28(8): 1700-1712 ; 11 www.nccn.org; 12 Krop I *et al.*, J Clin Oncol 2017; 35(24): 2838-2847 ; 13 Senkus E *et al.*, Ann Oncol 2015; 26 Suppl 5: v8-v30 ; 14 https://www.nice.org.uk/guidance/dg34; 15 Sestak I *et al.*, JAMA Oncol 2018; 4(4): 545-553