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Date of request: June 19, 2015

Re: NCCN Guidelines® Panel: Breast Cancer

On behalf of NanoString Technologies, I respectfully request the NCCN Breast Cancer Guideline Panel to consider the referenced clinical data as Level 1 evidence supporting the inclusion of the FDA-cleared[1] Prosigna® Breast Cancer Gene Signature Assay, as an option to inform adjuvant treatment decisions in patients with early-stage breast cancer (EBC).

Specific Changes: On page BINV-6, we request the addition of a footnote associated with the heading "Systemic Adjuvant Treatment-Hormone Receptor-Positive-HER2-Negative Disease" to read "Consider use of a PAM50 gene-expression assay (Prosigna) in conjunction with other clinicopathological factors to help guide adjuvant treatment decisions of hormone receptor-positive (HR+) lymph node-negative, Stage I or II breast cancer and HR(+), lymph node-positive (1–3 nodes), Stage II breast cancer (BC) patients.

Rationale: The basic rationale for including Prosigna in guidelines was outlined in a previously submitted request dated *06/20/2014*. Since that time new data have emerged confirming Prosigna's clinical validity and clinical utility for providing prognostic information on the rate of recurrence (0-5 years) and beyond 5 years in N(1-3) EBC patients.[2,3] Herein, we provide supplemental data on recent inclusion in international treatment guidelines, improvements in patient access, and data from the most important studies on Prosigna that were presented at ASCO 2015.

International Guidelines & Patient Access

Prosigna has been included in two updated international breast cancer guidelines, and has become broadly accessible to EBC patients in the U.S. and twelve other countries.[4,5] In the recently updated AGO guidelines, Prosigna was included with indication for newly diagnosed patients with node-negative or node-positive, HR+/HER2- EBC, for whom clinicopathological factors alone do not allow physicians to make a clear therapeutic decision.[4] Prosigna is recognized as being prognostic with Level 1B evidence.[4]

The 2015 St.Gallen International Breast Cancer Guidelines Panelists agreed that Prosigna/PAM50 and several other multi-parameter assays identify patients for whom prognosis is so favorable that even if chemotherapy is effective, the benefits of treatment are so small that they do not outweigh the risks. The panel also recognized the clinical utility of PAM50's prognostic score, noting that chemotherapy could be omitted in hormone receptor positive early-stage breast cancer patients with low PAM50 ROR scores even if clinicopathological variables suggested a higher risk of recurrence. Among all prognostic tests evaluated, PAM50 secured the highest percentage of panelist votes for being prognostic over the first five years following diagnosis (93% of panelists), and was the only test for which a majority of panelists recognized prognostic value more than five years after diagnosis.[5]

Finally, U.S. patient access to Prosigna has increased substantially. At least ten U.S. clinical laboratories are currently offering Prosigna testing, and another 9 labs are preparing for launch, including labs at 5 NCCN member institutions. In May, Palmetto GBA, a Medicare Administrative Contractor (MAC), issued a positive draft coverage determination for Prosigna through its MolDX program. This policy is expected to be finalized following the standard public comment period, increasing U.S. insurance coverage for Prosigna to ~65% of the post-menopausal breast cancer patients.

Newly Presented Data from ASCO 2015.

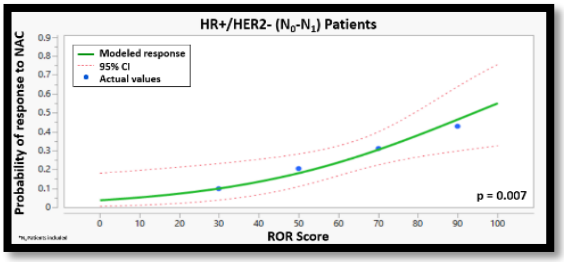
Prosigna is prognostic in a real-world setting

New data has recently demonstrated that the Prosigna ROR score provides additional prognostic information for distant recurrence on a large-sample size with a median follow-up of 10 years.[2,3] This study, conducted by the Danish Breast Cancer Group (DBCG), represents the first genomic study of breast cancer on a comprehensive nationwide population (2,722 patients).[6-8] The study included several pre-specified analyses, which were presented in three posters at the ASCO 2015 meeting, and which support the use of Prosigna to inform chemotherapy and endocrine therapy use.[6-8] In the first poster, the authors demonstrated that the use of the Prosigna ROR score improved prediction of 10-year DR and suggested that the ROR score can help identify N(0) and N(+) EBC patients who have an excellent prognosis and can avoid overtreatment with adjuvant chemotherapy.[6] In a second poster, based on an analysis of the results of the N(+) EBC patients, the authors concluded that Prosigna identifies a significant number of N(+) patients who have low risk of recurrence and may be spared chemotherapy.[7] Additional analyses demonstrate that both the continuous ROR score and the ROR risk categories added statistically significant prognostic information, thereby improving outcome prediction for patients with one ($P<0.0001$), two ($P<0.0001$), or three positive nodes ($P<0.008$).[7] In a third poster, based on an analysis of clinical outcomes during the second 5-years following the diagnosis of patients that were disease-free after 5-years of hormonal treatment, the Prosigna ROR score accurately reflected risk of DR, with High Risk having a 10.2%, Intermediate Risk having a 6.1%, and Low Risk having a 2.4% risk of late distant recurrence (DR). As a result, the authors concluded that Prosigna may be utilized to identify patients who need, or more importantly may be spared, extended endocrine therapy.[8]

Prosigna predicts which patients respond to chemotherapy

The chemosensitivity of Prosigna High Risk patients is implied by the high degree of overlap in the patient populations and similar Kaplan-Meir curves for the Prosigna and OncotypeDX High Risk groups previously observed in the TransATAC study. The chemosensitivity of Prosigna High Risk patients has now been confirmed in a second study presented at ASCO 2015, supporting Prosigna's clinical utility by verifying the ability of Prosigna to predict which patients respond to chemotherapy.[9] A manuscript describing this study is currently under final review by the journal of Clinical Cancer Research, and will be provided to the Committee once the paper is available.[10]

Figure 1.Prosigna's ability to predict the probability of response to NAC [9]

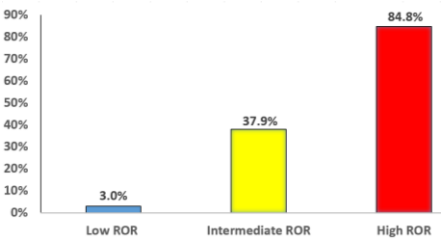


In this study, higher Prosigna ROR scores predicted increased rate of response to a modern neoadjuvant (NAC) chemotherapy regimen containing anthracyclines and taxanes in a population of HR+, HER2-, N0- and N(1-3) EBC patients (p=0.007). Prosigna's ROR score was shown to be predictive of chemosensitivity with tumors assigned Low Risk ROR scores being unresponsive to NAC. In node-negative and node-positive patients (1-3 positive nodes), Prosigna's ROR score was strongly associated with response to NAC (**Fig. 1**). For every 20-point increase in ROR score, a patient was 59% more likely to respond to chemotherapy in the neoadjuvant setting.[9] Response to NAC has been demonstrated to predict OS in patients with aggressive tumor subtypes.[11] For patients who are chemosensitive, outcomes are similar regardless of whether chemotherapy is given in the neoadjuvant or adjuvant settings, implying that Prosigna's ability to predict response to chemotherapy may be extended to the prediction of benefit in the adjuvant setting.[11,12]

Prosigna results change treatment decisions

In a third recent study, the WSG study group (Germany) presented data on the Prosigna Assay's impact on physicians' treatment decision and confidence.[13] Results from the Prosigna Assay changed the selection of chemotherapy in 18.2% of patients overall, including 39.2% of patients whose tumors was found to be luminal B subtype by Prosigna. Results mirror the observations of GEICAM study group (Spain), who recently published a similar study showing that Prosigna changed treatment recommendations in ~20% of patients while both increasing physicians confidence in the test and reducing patient anxiety (**Fig. 2**).[13,14]

Figure 2. A) Patients receiving chemotherapy.



B) Changes in physicians' recommendation post-Prosigna

	Low ROR		Intermediate ROR		High ROR		TOTAL	
	N=101	(%)	N=66	(%)	N=33	(%)	N=200	(%)
HT to CHT	0	(0.0)	9	(13.6)	9	(27.3)	18	(9.0)
CHT to HT	13	(12.9)	9	(13.6)	0	(0.0)	22	(11.0)
Total	13	(12.9)	18	(27.3)	9	(27.3)	40	(20.0)

Conclusion

In summary, the body of new clinical evidence published and presented over the past twelve months confirms in a real-world setting the observations from the clinical validation studies for Prosigna (TransATAC and ABCSG8) and greatly expands the evidence of clinical utility. In parallel, Prosigna has been incorporated into international treatment guidelines, and U.S. patient access is rapidly expanding, including within NCCN member institutions. We welcome any questions or clarifications that you may have.

References:

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