

Submitted by:

J. Wayne Cowens, M.D.
Chief Medical Officer
Nanostring Technologies, Inc.
530 Fairview Avenue N, Suite 2000
Seattle, WA 98109
Email: jwcowens@nanostring.com
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NCCN Guidelines Panel: Breast Cancer

On behalf of NanoString Technologies, I would like to request the NCCN Breast Cancer Guideline Panel to consider the enclosed data, which describe the use of the Prosigna® Breast Cancer Gene Signature Assay ("Prosigna assay") to inform treatment decisions in patients with early-stage breast cancer.

Specific Changes: We respectfully request the inclusion of the Prosigna assay in the treatment algorithm alongside other multi-analyte assay(s) that inform treatment decisions in hormone receptor positive (HR⁺) early-stage breast cancer, as well as the inclusion of a description of the Prosigna assay's analytical validation, clinical validation, and clinical utility in the discussion section.

FDA Clearance: The Prosigna assay^{1,2} and the nCounter® Dx Analysis System³ are FDA cleared for use in qualified clinical laboratories to assess the risk of distant recurrence in HR⁺, lymph node-negative and node-positive, women with early-stage breast cancer.

Rationale: The Prosigna assay, which measures the expression levels of the 50 genes in the PAM50 gene signature⁴ has been clinically validated to provide an accurate assessment of a patient's risk of distant recurrence in two independent prospectively planned, retrospective studies including a total of more than 2,400 patient samples (TransATAC^{8,10} and ABCSG-8^{9,10}) which together provide level 1b evidence of clinical validity.¹⁴

Supporting Information: The aforementioned clinical studies validate the Prosigna assay's ability to accurately identify an individual patient's 10-year risk of distant recurrence when treated with five years of hormone therapy alone.⁸⁻¹² This information has clinical utility for both the Low Risk population, where the event rate is so low (<4%) that a patient can safely be spared the adverse side effects of adjuvant systemic chemotherapy, and the High Risk population, where the potential benefit from adjuvant chemotherapy or extended endocrine therapy is high enough to outweigh the risk of serious adverse effects conferred by the use of systemic therapy.

The TransATAC study directly assessed the comparative effectiveness of the Prosigna assay versus the 21-gene Recurrence Score (RS) in a prospectively planned analysis of 1,017 patients using identical RNA samples. The investigators demonstrated that these tests have a concordance rate of 73% and 68% in the classification of patients as Low and High risk, respectively. The concordance rate in classification of patients as Intermediate risk was 28%. Based on the 10-year outcomes, they concluded that the Prosigna ROR score provided more prognostic information in endocrine-treated patients with ER⁺, node-negative disease compared to the 21-gene Recurrence Score, with better differentiation of the intermediate and higher-risk groups, resulting in 21% fewer patients being categorized as Intermediate Risk.⁸

The TransATAC study showed that Prosigna and the 21-gene RS identified a similar percentage (59%) of node-negative patients as Low Risk, and that these groups had a similar risk of recurrence (4%).⁸ The ABCSG-8 study showed that Prosigna identified a similar percentage of Low Risk patients, and the investigators concluded that these patients were unlikely to benefit from additional chemotherapy.^{6,9,11}

Conversely, the TransATAC study also showed that node-negative patients identified as High Risk by either Prosigna or the 21-gene RS had a 33% risk of recurrence at 10 years.⁸ Because chemotherapy provides the 30-35% average relative risk reduction as established by the EBCTCG data, this population would be expected to see a significant improvement in distant recurrence free survival at 10 years. For these High Risk patients, the potential for benefit from adjuvant chemotherapy outweighs the risk of serious adverse side effects conferred by this treatment.^{9,13}

Identifying biomarkers which predict the risk of late recurrence was identified as a research priority in the recently updated ASCO Guidelines for use of systemic therapy in EGFR2 Breast Cancer. In published analyses of both the TransATAC and

ABCSG-8 studies, the Prosigna assay discriminated patients into groups at low-risk and high-risk for late distant recurrence.^{11,12} The investigators of these studies concluded that Prosigna may help select patients who could benefit most from or, alternatively, be spared the need for hormonal therapy beyond 5 years of treatment.^{11,12}

Finally, rigorous analytical validation has demonstrated highly concordant Prosigna assay results across multiple clinical laboratory sites, technicians, and manufacturing lots of Prosigna reagents, supporting the decentralized use of the Prosigna assay⁷. The FDA cleared Prosigna assay is currently available through national commercial laboratories, and will soon be available from leading academic and community cancer centers.¹

We gratefully acknowledge the contributions of NCCN panel members, some of whom are also co-authors or co-contributors to these publications. If you have any questions or require additional information, please do not hesitate to contact me at 206-552-2700 or via e-mail at jwcowens@nanosttring.com. Thank you for your time and consideration.

Sincerely,

J. Wayne Cowens, M.D.
Chief Medical Officer
NanoString Technologies, Inc.

Prescribing Information:

1. US Package Insert, updated November 2013
2. CE Package Insert (European Union, Israel, and Canada*), updated August 2013, *Canadian licensure received in May 2014

nCounter Platform, Intrinsic Subtype and PAM50 assay development:

3. Geiss GK, et al. Direct multiplexed measurement of gene expression with color-coded probe pairs. *Nat Biotechnol.* 2008; 26(3):317-325.
4. Parker JS, et al. Supervised risk predictor of breast cancer based on intrinsic subtypes. *J Clin Oncol.* 2009; 27(8):1160-1167.
5. Perou CM, et al. Molecular portraits of human breast tumors. *Nature.* 2000;406(6797):747-752.
6. Nielsen TO, et al. A comparison of PAM50 intrinsic subtyping with immunohistochemistry and clinical prognostic factors in Tamoxifen-treated estrogen receptor-positive breast cancer. *Clin Cancer Res.* 2010;16(21): 5222-5232.

Analytical validation:

7. Nielsen T, et al. Analytical validation of the PAM50-based Prosigna Breast Cancer Prognostic Gene Signature Assay and nCounter Analysis System using Formalin-fixed paraffin-embedded breast tumor specimens. *BMC Cancer.* 2014;14(1):177.

Clinical validation in the adjuvant endocrine therapy setting:

8. 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(22):2783-2790.
9. Gnant M, et al. Predicting distant recurrence in receptor-positive breast cancer patients with limited clinicopathological risk: using the PAM50 score in 1,478 postmenopausal patients of the ABCSG 08 trial treated with adjuvant endocrine therapy alone. *Ann Oncol.* 2014;25(2):339-345.
10. Gnant M, et al. Identifying clinically relevant prognostic subgroups in node-positive postmenopausal HR+ early breast cancer patients treated with endocrine therapy: a combined analysis of 2,485 patients from ABCSG-8 and ATAC using the PAM50 risk of recurrence (ROR) score and intrinsic subtype. Presented at: 2013 ASCO Annual Meeting; May 31-June 4, 2013; Chicago, IL. Abstract 506. **(Includes Risk stratification of node-positive patients)**

Predicting the risk of late recurrence (beyond 5 years)

11. Filipits M, et al. The PAM50 risk-of-recurrence score predicts risk for late distant recurrence after endocrine therapy in postmenopausal women with endocrine-responsive early breast cancer. *Clin Cancer Res.* 2014;20(5):1298-305.
12. Sestak I, et al. Factors predicting late recurrence for estrogen receptor-positive breast cancer. *J Natl Cancer Inst.* 2013;105(19):1504-1511.

Evidence standards for molecular diagnostics

13. Hayes DF. From genome to bedside: are we lost in translation? *Breast.* 2013;22(suppl 2):S22-S26.
14. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. *J Natl Cancer Inst.* 2009;101(21):1446-1452.