

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 to support the FDA-cleared¹ Prosigna[®] Breast Cancer Gene Signature Assay, as an option to be considered to help assess risk of recurrence and predict response to chemotherapy in post-menopausal women with hormone receptor positive early stage breast cancer (EBC). Based on new clinical information developed and guidelines adopted for PAM50-based Prosigna gene signature assay, we are requesting the following changes to the NCCN guidelines.

Specific Changes:

- I. On page BINV-6, we request to modify the decision tree/treatment algorithm by including the PAM50 gene signature assay in assessing the risk of recurrence and selection of adjuvant therapy, or alternatively, recommend only a footnote “**dd**” without highlighting any specific assay(s) in the decision tree/treatment algorithm.
- II. On page MS-29 to include information on the 510K FDA clearance of the PAM50 assay.
- III. On page MS-29, we request to update the information to uniformly identify the 50-gene assay as a PAM50 gene signature assay.
- IV. On page MS-29 to include information that PAM50-based intrinsic breast cancer subtypes are prognostic independent of standard clinical factors (based on analysis from CALGB 9741)¹²

Rationale: The rationale for updating Prosigna (PAM50) information in the guidelines is based on requests dated *06/20/2014 and 06/19/2015*. Since that time new data have emerged confirming Prosigna's clinical validity and clinical utility for providing prognostic and predictive information.^{2-6,12-14} In the past 12 months major breast cancer treatment guidelines (AGO, SEOM, St. Gallen, ESMO, Japanese Breast Cancer Society, and ASCO) included Prosigna (PAM50) for its prognostic and predictive value. Additional data was published confirming the prognostic ability of Prosigna (PAM50)-based intrinsic subtypes independent of clinical factors.¹² These updates underscore the significant body of evidence demonstrating Prosigna's clinical validity and clinical utility, and further strengthen the case for a corresponding update in the next version of the 2016 NCCN guidelines.

ASCO Breast Cancer Guidelines Update (2016)

The American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines provide evidence-based recommendations and recommend Prosigna (PAM50) to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer with known hormone receptor and HER2 status.⁷ Specifically, it states that “chemotherapy should be considered in the PAM50 high-risk group, but is not indicated in patients in the low-risk group.”⁷

In parallel, the ASCO guidelines included a subtle but powerful critique of the “prediction studies” that have historically been the foundation of the privileged positioning of the OncotypeDX (21-gene assay) within treatment guidelines. For example, in the section “Recommendation 1.2”, the ASCO Committee states: “However, the B20 data are confounded by the data set originally used to generate the 21-gene RS algorithm. The results from SWOG S8814 must be considered hypothesis generating because the number of samples analyzed in each RS subgroup was small, there was no additional prediction beyond 5 years, and the risks of systemic recurrence continues to be high for patients with node-positive disease.” On page 19 of the Data Supplement, the ASCO Committee characterized the conclusion that the B20 study showed chemoprediction as “highly speculative”.

The Prosigna (PAM50) gene signature assay received a “high” rating of evidence quality together with a “strong” recommendation, making the evidence quality and strength of recommendation the highest among all genomic assays reviewed and equal to that of OncotypeDx (21-gene assay).⁷ We believe that this argues strongly for eliminating any distinction between the ways that these assays are represented in the decision tree/treatment algorithm on *BINV-6*.

Other Recent Breast Cancer Treatment Guideline Updates

Prosigna (PAM50) has also been included in two updated international breast cancer guidelines (ESMO, Japanese Breast Cancer GLs), and has become broadly accessible to EBC patients in the U.S. and twelve other countries.^{8,9} In the recently updated ESMO guidelines, Prosigna has been recognized with Level IB evidence and has been recommended for use in the determination of patient prognosis and for selection of optimal adjuvant therapy in the intended patient population. These guidelines stated that Prosigna can determine the individual's recurrence risk as well as potentially predict the benefit of chemotherapy in that patient population.⁸ Similar to the ASCO guidelines, the ESMO guidelines place Prosigna (PAM5) at the highest level of evidence for any assay, and make no distinction between its positioning and that of OncotypeDX (21-gene assay).

Newly Presented Data from SABCS 2015

Prosigna's ROR score was demonstrated as a strong predictor of response to taxane

Prosigna's Risk of Recurrence (ROR) score was demonstrated as a strong predictor of response to taxane and anthracycline-based neoadjuvant chemotherapy (NAC) in a representative cohort of EBC patients including HR+/HER2- N0-N1 patients.^{4,5} Given that the ROR score is partially derived from the correlation of the tumor's expression profile to that of the four prototypical intrinsic subtypes as well as its proliferative capacity in a representative cohort of 294 breast cancer patients, both the magnitude of the subtype correlation to the prototypical centroids as well as P-score, as determined by the Prosigna algorithm, were strong predictors of response to NAC (Fig. 1).⁶ Response to NAC has been demonstrated to predict overall survival (OS) in patients with aggressive breast cancer subtypes.¹⁰

For breast cancers which are chemosensitive, patients' 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.^{10,11}

Correlative Analysis of CALGB 9741 (Alliance)

Tumor analysis from the CALGB 9741 (n=2,104) adjuvant node-positive breast cancer trial demonstrated that Prosigna (PAM50) intrinsic breast cancer subtypes are prognostic independent of standard clinicopathologic factors even in a clinically high risk patient population treated with adjuvant chemotherapy.¹² It was shown that the highly prognostic value of PAM50 intrinsic subtype was greater than ER/HER2 immunohistochemistry classification and was also independent of menopausal status.¹² The Prosigna (PAM50) ROR score and intrinsic subtype were strongly associated with relapse-free survival (RFS) and OS in both treatment groups independent of clinical factors. These findings support the clinical validity of Prosigna (PAM50) in node-positive, pre- and post-menopausal early-stage breast cancer patients.¹²

Conclusion

In summary, the body of new clinical evidence published and presented over the past 12 months confirms the observations from the original clinical validation studies for Prosigna (PAM50) (TransATAC and ABCSG8) and expands the evidence of clinical utility. In parallel, Prosigna (PAM50) has been incorporated into international and domestic treatment guidelines, at the highest levels of evidence awarded for any assay and strengths of recommendation that match that of OncotypeDX (21-gene assay). U.S. patient access has rapidly expanded to cover 80% of the indicated patient population, with Medicare coverage in all 50 states and positive medical policies from major private insurers such as United Healthcare, Aetna, and Cigna. Based on all of these factors, we believe that Prosigna (PAM50) should be included in the NCCN guidelines, positioned on par with other assay(s) at the highest levels of evidence for clinical validity or utility. We welcome any questions or clarifications that you may have.

References:

1. NanoString. Prosigna Breast Cancer Prognostic Gene Signature Assay. In: Nanostring, ed: Package Insert; 2015.
2. Gnant M, et al. Ann Oncol 2015 Aug;26(8):1685-91.
3. Sestak I, et al. J Clin Oncol. 2015;33(8):916-22.
4. Rodriguez B, et al. J Clin Oncol 33, 2015 (suppl; abstr 11049).
5. Prat A, et al. Clin Cancer Res 2016 Feb 1;22(3):560-6.
6. Chica Parrado R, et al. Cancer Res 2016 February 15, 2016;76(4 Supplement):P3-07-15.
7. Harris LN, et al. J Clin Oncol 2016 Feb
8. Senkus E, et al. Ann Oncol 2015 September 1, 2015;26(suppl 5):v8-v30.
9. Aihara T, et al. Breast Cancer 2016 Feb 24
10. Cortazar P, et al. Lancet. 2014;384(9938):164-72.
11. Gianni L, et al. J Clin Oncol. 2009;27(15):2474-81
12. Liu MC, et al. Npj Breast Cancer 2016 01/06/online;2:15023.

Figure 1. Probability of response according to P-score.⁶

