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NCCN Guidelines Panel: Breast Cancer

On behalf of Genomic Health, Inc., I respectfully request that the **NCCN Breast Cancer Panel** review the enclosed data for inclusion of the **Oncotype DX® Breast Recurrence Score™** (RS) assay, also known as the 21-gene RT-PCR assay, for the prediction of chemotherapy (CT) benefit of patients with node-negative (N0), hormone receptor-positive (HR+), HER2-negative early breast cancer (EBC).[1,2]

Specific Changes: Remove the word **"consider"** from the pN0 and pN1mi (micrometastatic) component of the invasive breast cancer algorithm (BINV-6).

FDA Clearance: FDA clearance is not required for this assay because the assay is performed in the central laboratory at Genomic Health that is regulated and certified under the Clinical Laboratory Improvement Amendments (CLIA) and the College of American Pathologists (CAP).

Rationale: The reporting of prospective outcomes from multiple datasets, including the RS <11 arm of TAILORx,[3] the WSG PlanB trial (RS <12),[4,5] the Israeli Clalit registry (RS <18),[6,7] and the SEER/NCI analysis (RS <18) that include >38K ER+, EBC patients treated based on the RS result,[8] is definitive evidence that the 21-gene RT-PCR assay identifies patients who should not be treated with and do not benefit from CT. In addition, based on these four studies, the 8th edition of the AJCC is now exclusively utilizing the 21-gene RT-PCR assay to downstage patients with T1/T2, N0, M0, ER+, HER2-negative EBC as high as IIIA down to IA, if they have RS <11.[9] This underscores the importance of having the 21-gene RT-PCR assay RS information on every appropriate patient as part of the standard diagnostic and staging work-up prior to treating with systemic therapy.

The following articles are submitted in support of this proposed change:

1. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med.* 2004;351(27):2817-2826. [NSABP B-14; validation of the 21-gene RT-PCR assay for prognosis]
2. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol.* 2006;24(23):3726-3734. [NSABP B-20; validation of the 21-gene RT-PCR assay for prediction of CT benefit]
3. Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med.* 2015;373(21):2005-2014. [TAILORx; prospective, 5-year outcomes for RS <11]
4. Gluz O, Nitz UA, Christgen M, et al. West German Study Group phase III PlanB trial: First prospective outcome data for the 21-gene Recurrence Score assay and concordance of prognostic markers by central and local pathology assessment. *J Clin Oncol.* 2016;34(20):2341-2349. [PlanB; prospective 3-year outcomes for RS <12]
5. Nitz U, Gluz O, Christgen M, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial. *Breast Cancer Res Treat*. 2017. doi: 10.1007/s10549-017-4358-6. [Epub ahead of print]. [PlanB; prospective 5-year outcomes for RS <12]
6. Stemmer SM, Steiner M, Rizel S, et al. Real-life analysis evaluating 2028 N0/Nmic breast cancer patients for whom treatment decisions incorporated the 21-gene Recurrence Score result: 5-year KM estimate for breast cancer specific survival with recurrence score results ≤30 is >98%. *Cancer Res.* 2016;76(4 Supplement):P5-08-02. [Clalit; real-world, prospective 5-year outcomes for RS <18]

7. Stemmer SM, Steiner M, Rizel S, et al. Clinical outcomes in patients with node-negative breast cancer treated based on the Recurrence Score results: Evidence from a large prospectively designed registry. *npj Breast Cancer.* 2017:[manuscript in press]. [Clalit; real-world, prospective 5-year outcomes for RS <18]
8. Petkov VI, Miller DP, Howlader N, et al. Breast-cancer-specific mortality in patients treated based on the 21-gene assay: a SEER population-based study. *npj Breast Cancer.* 2016;2:16017. [SEER/NCI; real-world 5-year outcomes for RS <18]
9. Hortobagyi GN, Connolly JL, D'Orsi CJ, et al. Breast. In: Amin MB, Edge S, Greene F, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer Publishing; 2017:589-628. [use of the 21-gene RT-PCR assay (RS <11) to downstage patients with EBC to prognostic stage IA]

Sincerely,

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