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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 publications for inclusion of the **Oncotype DX Breast Recurrence Score®** (RS) assay, also known as the 21-gene RT-PCR assay, for decision-making of optimal pre-operative systemic therapy for women with operable ER+, HER2 (-) invasive breast cancer.

Specific Changes: Add the use of the 21-gene RT-PCR in the preoperative work-up in women with ER+, HER2(-) breast cancer during the work-up of the patient as reflected in BINV-10. Add language in BINV-L as follows: Preoperative endocrine therapy alone may be considered for patients with ER+, HER2(-) breast cancer with a 21-gene RT-PCR assay result that has been shown to predict for a lack of chemotherapy benefit when given in the adjuvant setting.

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 original prospective-retrospective validation trial NSABP B-20[2] demonstrated that the 21-gene Recurrence Score was not only prognostic for distant recurrence in women treated with tamoxifen alone, but was predictive of chemotherapy benefit for women with a RS $\geq$31. When considering the 6711 eligible patients with a RS 11-25, the 9-year DFS and distant recurrence curves showed no benefit to adding chemotherapy to endocrine therapy in the primary analysis. The level 1A evidence from TAILORx suggests that women with ER+, HER2 (-) breast cancer should have a 21-gene RT-PCR assay for optimal systemic therapy decision-making regardless of whether it is in the pre-operative or adjuvant setting to avoid overtreating with chemotherapy in those with a low RS and undertreating with endocrine therapy alone in those with a high RS.

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 and Paik S. Development of the 21-gene assay and its application in clinical practice and clinical trials. *J Clin Oncol.* 2008;26(5):721-728. [NSABP B-20 data analyzed using RS ranges used in TAILORx]
4. Sparano JA, Gray RJ, Makower, KI, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med*. 2018. Doi: 10.1056/NEJMoa1804710. [Epub ahead of print]. [TAILORx 9-year data with outcomes from women with RS$\leq$11, RS 11-25, and RS $\geq$26]
5. Akashi-Tanaka S, Shimizu C, Ando M, et al. 21-Gene expression profile assay on core needle biopsies predicts responses to neoadjuvant endocrine therapy in breast cancer patients. *The Breast.* 2009;18:171-174. [Retrospective correlation with RS and response in women prospectively receiving preoperative endocrine therapy]

6. Ueno T, Masuda N, Yamanaka T, et al. Evaluating the 21-gene assay Recurrence Score® as a predictor of clinical response to 24 weeks of neoadjuvant exemestane in estrogen recepton-positive breast cancer. *Int J Clin Oncol.* 2014;19(4):607-613. [Association between the RS assay and the clinical response to neoadjuvant endocrine therapy]
7. Bear HD, Wan W, Robidoux A, et al. Using the 21-gene assay from core needle biopsies to choose neoadjuvant therapy for breast cancer: A multicenter trial. *J Surg Oncol*. 2017;115(8):917-923. [Neoadjuvant therapy prospectively determined by 21-gene Recurrence Score]

Sincerely,

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