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NCCN Guidelines Panel: Breast Cancer

On behalf of Genomic Health, Inc., I respectfully request the **NCCN Breast Cancer Panel** to review the enclosed data for inclusion of the **Oncotype DX® Breast Recurrence Score™** (RS) assay, also known as the 21-gene RT-PCR assay, in the initial work-up for patients diagnosed with early stage ER+, HER2-negative, lymph node-positive (1-3 nodes) breast cancer, to stratify patients by risk of recurrence and identify patients with likely chemotherapy benefit.

Specific Changes: Elevate the 21-gene RT-PCR assay from “footnote ee” on page BINV-6 to the clinical algorithm as a component of the initial work-up for patients after diagnosis with early stage ER+, HER2-invasive breast cancer with 1-3 positive lymph nodes, in a manner consistent with use of the 21-gene RT-PCR assay for node-negative patients (BINV-6).

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

Rationale: In support of these changes, the 21-gene RT-PCR assay was validated in node-positive patients in two prospectively designed studies to predict risk of distant recurrence and identify patients who are likely to benefit from chemotherapy.^{1,2} More recently, prospective outcomes in >7K node-positive patients (1-3 positive nodes) have been reported in three cohorts, including the WSG PlanB study showing 3- and 5-year disease free survival data,^{3,4} the SEER registry showing 5-year breast cancer specific mortality data,^{5,6} and the Israeli Clalit registry showing 5-year distant recurrence data.^{7,8} All of these studies show that patients with low RS results have highly favorable outcomes when treated with endocrine therapy alone, providing strong and consistent support that the 21-gene RT-PCR assay provides important prognostic information in node-positive disease.

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

1. Dowsett M, Cuzick J, Wale C, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. *J Clin Oncol*. 2010;28(11):1829-1834. [[TransATAC; validation of the 21-gene RT-PCR assay for prognosis](#)]
2. Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol*. 2010;11(1):55-65. [[SWOG 8814; validation of the 21-gene RT-PCR assay for prediction of chemotherapy benefit](#)]
3. 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](#)]
4. 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](#)]

5. Roberts MC, Miller DP, Shak S, Petkov VI. Breast cancer-specific survival in patients with lymph node-positive hormone receptor-positive invasive breast cancer and Oncotype DX Recurrence Score results in the SEER database. *Breast Cancer Res Treat.* 2017;163(2):303-310. [[SEER/NCI; real-world 5-year outcomes for RS <18](#)]
6. 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](#)]
7. Stemmer SM, Steiner M, Rizel S, et al. Clinical outcomes following Recurrence Score-based therapy in N+ ER+ breast cancer: a cohort study. *Breast.* 2017;32(1 suppl):S106. [[Clalit; real-world, prospective 5-year outcomes for RS <18](#)]
8. Stemmer SM, Steiner M, Rizel S, et al. Clinical outcomes in ER+ HER2- node-positive breast cancer patients who were treated according to 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](#)]

Sincerely,

A handwritten signature in black ink, reading "Christy A. Russell, MD". The signature is fluid and cursive, with the first name "Christy" being the most prominent part.

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Genomic Health, Inc.