

Christy A. Russell, MD; Senior Director, Medical Affairs Genomic Health, Inc. 301 Penobscot Drive, Redwood City, CA 94063 Phone: (650) 599-4394 | E-mail: <u>CRussell@genomichealth.com</u> July 3, 2018

NCCN Guidelines Panel: Breast Cancer

On behalf of Genomic Health, Inc., I respectfully request, based on the publications listed below, that the **NCCN Breast Cancer Panel** update the NCCN Guidelines for 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}

<u>Specific Changes</u>: Remove the word "**consider**" from the pN0 and pN1mi (micrometastatic) component of the invasive breast cancer algorithm (BINV-6), add a notation of (category 1), and indicate in a footnote "for those eligible for chemotherapy". Change the specific treatment recommendations based on the Recurrence Score result to the TAILORx-defined cutpoints for chemotherapy benefit.

<u>FDA Clearance</u>: 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-20² demonstrated that the 21gene 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 >31. TAILORx was designed to determine the effect of chemotherapy, if any, for patients Recurrence Score result of intermediate risk³. The investigators, with patient and advocate input, adjusted the Recurrence Score cutoffs to avoid undertreatment. The cutoff for 26 was selected based on an analysis of NSABP B-20, which demonstrated a large chemotherapy benefit³. Patients with a RS 11-25 (two-thirds of all patients) were randomly assigned to endocrine therapy alone or endocrine therapy plus chemotherapy⁴. Those with a RS 0-10 received 5 years of endocrine therapy alone, and those with a RS 26-100 received endocrine therapy plus chemotherapy. 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 for all women >50 years of age with a RS up to 25. For women \leq 50 years of age, there was no benefit from the addition of chemotherapy up to a RS of 15. A minimal (1-2 percent) benefit from chemotherapy was observed with Recurrence Score results of 16 to 20, which gradually grew as scores increased up to 25. The level 1A evidence from TAILORx suggests that women with ER+, HER2 (-), lymph node-negative breast cancer who are eligible for chemotherapy should have an Oncotype DX Recurrence Score prior to a decision being made for optimal systemic adjuvant therapy.

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

- 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≤11, RS 11-25, and RS ≥26]

Sincerely,

a. soele. 20

Christy Russell, MD Senior Director, Medical Affairs Genomic Health, Inc.