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NCCN Guidelines Panel: Breast Cancer

On behalf of Exact Sciences, I respectfully request that the NCCN Breast Cancer Panel review the enclosed publications for inclusion of the Oncotype Dx Breast Recurrence Score® 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 operable ER+, HER2(-) breast cancer if she is under consideration for neoadjuvant systemic therapy, as reflected in BINV-11. Add language in BINV-M as follows: Preoperative endocrine therapy alone may be considered for patients with ER+, HER2(-) breast cancer with a 21-gene RT-PCR assay result <18 that has been shown to significantly improve breast conserving surgery rates without evidence of progression, and for whom there is no adjuvant systemic chemotherapy benefit for both N0 and N1 disease.

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

Rationale: The Oncotype Dx Breast Recurrence Score® assay is both prognostic and predictive of chemotherapy benefit in the adjuvant setting for women with ER+, HER2(-), N0-N1 early breast cancer[1,2,3,4]. The prospective TransNEOS trial has validated the use of the assay in the neoadjuvant endocrine therapy setting, showing a lack of progressive disease as well as a substantial improvement in breast conserving surgery for those women with a low Recurrence Score® result[5]. There is also strong assay result concordance between core biopsies and excisional specimens[6]. These data led to the recommendation to consider the use of the assay by the COVID-19 pandemic breast cancer consortium in the neoadjuvant endocrine therapy setting[7].

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]

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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, KI, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med*. 2018; 379:111-121. [TAILORx 9-year data with outcomes from women with RS<11, RS 11-25, and RS >26]

4. 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 randomized trial. *Lancet Oncol* 2010; 11:55-65. [SWOG 8814 10-year validation of the 21-gene RT-PCR assay for prediction of chemotherapy benefit in N+ postmenopausal women]

5. Iwata H, Masuda N, Yamamoto Y, et al. Validation of the 21-gene test as a predictor of clinical response to neoadjuvant hormonal therapy for ER+, HER2-negative breast cancer: the TransNEOS study. *Breast Cancer Res Treat*. 2019; 173(1):123-133. [Validation of the 21-gene RT-PCR assay for prediction of neoadjuvant endocrine therapy]

6. Jakubowski DM, Bailey H, Abran J, et al. Molecular characterization of the breast cancer needle core biopsy specimens by the 21-gene Breast Recurrence Score test. *J Surg Oncol*. 2020. Doi: 10.1002/jso.26050. [Retrospective comparative analysis of >900,000 21-gene RT-PCR scores comparing core needle biopsy to excisional specimens]

7. Dietz JR, Moran MS, Isakoff SJ, et al. Recommendations for prioritization, treatment and triage of breast cancer patients during the COVID-19 pandemic. The COVID-19 pandemic breast cancer consortium. *Breast Cancer Res Treat*. 2020; 181:487-497. [Discusses options for management of neoadjuvant endocrine therapy in women with ER+, HER2-, N0-N1 early breast cancer including testing with the 21-gene RT-PCR score]