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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 12-gene **Oncotype DX® Breast DCIS Score™** assay in the initial work-up for patients diagnosed with DCIS, to stratify patients by risk of local recurrence (any or invasive), following lumpectomy with negative margins but prior to the decision or recommendation for radiation therapy.

Specific Changes: Include the 12-gene DCIS Score™ assay as a component of the initial work-up for patients diagnosed with DCIS, following lumpectomy with negative margins (page DCIS-1)

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 the proposed change, the 12-gene DCIS Score assay was validated in two prospectively designed studies to predict 10-year risk of any or invasive local recurrence in patients with DCIS after breast-conserving surgery alone (BCS)[1,2] or after BCS plus radiation therapy.[3] DCIS Score results added information beyond what was discerned by clinicopathologic factors alone.[1-3] Estimates of 10-year risk of local recurrence were further refined in a meta-analysis that combined both BCS-alone studies, showing that 47% of patients can be identified with a ≤10% risk of local recurrence over 10 years.[4] Subsequent to that publication, further prediction modeling was done including 1102 cases of DCIS comparing clinicopathologic features (CPF) versus CPF + ER and HER2, versus CPF + 12-gene DCIS score (DS). Individual prediction of locoregional recurrence (LR) incorporating CPF and DS was more accurate and identified a higher proportion of women with a low predicted risk of LR after BCS alone, for whom radiotherapy may be omitted.[5]

Shared decision-making in healthcare is realized when both patient and physician contribute to care decisions based on available information. In this capacity, the individualized risk estimates provided by DCIS Score results can support shared decision-making, such that patients can avoid radiation-related morbidity when their risk of recurrence is low or feel confident in their decision to have radiation therapy when their risk of recurrence is high. In support of the clinical utility of the DCIS Score assay, physicians in two prospective, multicenter decision impact studies changed recommendations for radiation therapy for about 30% of their patients, based on DCIS Score results.[6,7] In addition, a recent publication of ECOG E1142 trial showed that for women who underwent BCS for DCIS, 93% were adherent to the recommendation either supporting or discouraging the use of radiation therapy based on the 12-gene DCIS score result.[8]

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

1. Solin LJ, Gray R, Baehner FL, et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. *J Natl Cancer Inst.* 2013;105(10):701-710. [E5194; validation of the DCIS Score assay in a BCS-alone cohort]
2. Rakovitch E, Nofech-Mozes S, Hanna W, et al. A population-based validation study of the DCIS Score predicting recurrence risk in individuals treated by breast-conserving surgery alone. *Breast Cancer Res*

Treat. 2015;152(2):389-398. [Ontario study; validation of the DCIS Score assay is a BCS-alone cohort]

3. Rakovitch E, Nofech-Mozes S, Hanna W, et al. Multigene expression assay and benefit of radiotherapy after breast conservation in ductal carcinoma in situ. *J Natl Cancer Inst.* 2017;109(4). [Ontario study; validation of the DCIS Score assay is a BCS plus radiation therapy cohort

4. Rakovitch E, Gray R, Baehner FL, et al. Refined estimates of local recurrence risks by DCIS score adjusting for clinicopathological features: a combined analysis of ECOG-ACRIN E5194 and Ontario DCIS cohort studies. *Breast Cancer Research and Treatment.* 2018;169(2):359-369. [Meta-analysis of DCIS Score assay in two combined BCS-alone cohorts]

5. Paszat L, Sutradhar R, Zhou L, Nofech-Mozes S, Rakovitch E. Including the Ductal Carcinoma-In-Situ (DCIS) score in the development of a multivariable prediction model for recurrence after excision of DCIS. *Clin Br Ca*. 2019;19(1):35-46. [Multivariable prediction model for recurrence after excision of DCIS]

6. Alvarado M, Carter DL, Guenther JM, et al. The impact of genomic testing on the recommendation for radiation therapy in patients with ductal carcinoma in situ: A prospective clinical utility assessment of the 12-gene DCIS score result. *J Surg Oncol.* 2015;111(8):935-940. [Prospective decision impact study]

7. Manders JB, Kuerer HM, Smith BD, et al. Clinical utility of the 12-gene DCIS Score assay: impact on radiotherapy recommendations for patients with ductal carcinoma in situ. *Ann Surg Oncol.* 2016;24(3):660-668. [Prospective decision impact study]

8. Lehman CD, Gatsonis C, Romanoff J, Khan SA, et al. Association of magnetic resonance imaging with a 12-gene expression assay with breast ductal carcinoma in situ treatment. JAMA Oncology. 2019;5(7):1036-1042. [Data from ECOG E1142 showing physician and patient adherence to no-radiation recommendation with a low 12-gene DCIS score assay result]

Sincerely,

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Genomic Health, Inc.