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NCCN Guidelines panel: Breast Cancer Treatment

Dear NCCN Breast Cancer Treatment Panel members,

On behalf of Myriad Genetic Laboratories, Inc., I respectfully request your review of the enclosed request for modifications within the Breast Cancer guideline, Version 5.2020 - July 15, 2020.

Specific changes requested:

1. **BINV-6:**

- a. Please change wording in the decision tree from “Strongly consider 21-gene RT-PCR assay (category 1)<sup>kk,ll</sup>” to “Consider 21-gene RT-PCR assay (category 1) or 12-gene RT-PCR assay (category 2A)<sup>kk,ll</sup>”.
- b. In the decision tree we request that “EPclin Low ( $\leq 3.3$ )” be added under RS <26 and “EPclin High (>3.3)” be added under RS  $\geq 31$ .

2. **BINV-7:**

- a. To footnote “nn” please add the underlined text: “Regarding the 21-gene assay (OncotypeDx), a secondary analysis of a prospective trial (cohort of 367 women from SWOG-8814) suggests that the test is predictive for women with 1-3 involved ipsilateral axillary lymph nodes (category 2A). Regarding the 12-gene assay (EndoPredict), a secondary analysis of prospective trials (including chemo-endocrine (GEICAM 2003-02/9906) and endocrine only cohorts (ABCSG 6/8, TransATAC) with 1,284 women with node positive disease), suggests that EPclin High risk scores are predictive of chemotherapy benefit for women with nodal involvement (category 2A).<sup>1</sup>”

3. **BINV-N (1 of 4):** In the table, regarding the row for the 12-gene (EndoPredict) assay:

- a. In the “Predictive” column, please change “Not determined” to “Yes” for the 12-gene (EndoPredict) assay.
- b. In footnote “a” please add the underlined text to the sentence: “The 21-gene assay (OncotypeDx) is preferred by the NCCN Breast Cancer Panel for node-negative breast cancer (category 1). The 12-gene assay (EndoPredict) is also predictive of chemo-benefit in both node-negative and node-positive breast cancer (category 2A).”

4. **BINV-N (3 of 4):** In the table, regarding the row for the 12-gene (EndoPredict) assay:

- a. To the end of the Treatment Implications paragraph, please add the following sentence: “Chemo-prediction has also been demonstrated in other studies in both the adjuvant<sup>2</sup> and neoadjuvant setting.<sup>3,4,5</sup>”
- b. Please correct the Recurrence Risk column wording from “Low (<3.33)” and “High (>3.33)” to “EPclin Low ( $\leq 3.3$ )” and “EPclin High (>3.3)”.
- c. An incorrect reference is provided for the sentence “For patients with T1 and T2 hormone receptor-positive, HER2-negative and lymph node-negative tumors...<sup>13</sup>”. The correct reference is *Filipits M, Rudas M, Jakesz R et al., 2011*.<sup>6</sup> For the next sentence “In ABCSG 6/8, patients in the low-risk group had risk...<sup>13</sup>”, the correct references are *Filipits M, Rudas M, Jakesz R et al., 2011*<sup>6</sup> and *Sestak I, Buus R, Cuzick J, et al., 2018*.<sup>7</sup>

FDA Clearance: Not applicable

Rationale per above bullets:

- 1-3: The guidelines correctly state on BINV-N (3 of 4) under “Treatment Implications” for the 12-gene (EndoPredict) assay that “The risk score is predictive of chemo-benefit based on a prospective analysis of 3,746 archived, HR-positive, HER2-negative, T1-T3 tumors from chemo-endocrine and endocrine-only cohorts, that included women with lymph node-negative and lymph node-positive disease”. This statement correctly indicates the chemopredictive ability of the 12-gene EndoPredict assay.<sup>1,6</sup> However, this chemopredictive ability is not consistently acknowledged in the guideline subsections referenced above.
- 4a: Justification for inclusion of this sentence is based on four publications, three that are very recent.<sup>2,3,4,5</sup>
- 4b: The 12-gene test reports an EP molecular score based on gene expression alone *and* an EPclin score that incorporates tumor size and nodal status. Although the molecular score is validated for accurate prognosis, the EPclin score provides greater prognostic ability. It is important and accurate to clarify “EPclin” and to state “3.3” (not “3.33”) and include “≤” and “>” in the correct locations.
- 4c: The references are provided below.

References:

1. Sestak I, Martin M, Dubsky P, et al. Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone. *Breast Cancer Res Treat.* 2019; 176(2):377-386.
2. Soliman H, Flake DD, Magliocco A, et al. Predicting expected absolute chemotherapy treatment benefit in women with early-stage breast cancer using EndoPredict, an integrated 12-gene clinicomolecular assay. *JCO Precis Oncol.* 2019 3(3):1-10
3. Dubsky PC, Singer CF, Egle D, et al. The EndoPredict score predicts response to neoadjuvant chemotherapy and neoendocrine therapy in hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer patients from the ABCSG-34 trial. *Eur J Cancer.* 2020; 134:99-106.
4. Soliman H, Wagner S, Flake DD, et al. Evaluation of the 12-gene molecular score and the 21-gene recurrence score as predictors of response to neo-adjuvant chemotherapy in estrogen receptor-positive, HER2-negative breast cancer. *Ann Surg Oncol.* 2020; 27:765-771.
5. Bertucci F, Finetti P, Viens P, et al. EndoPredict predicts for the response to neoadjuvant chemotherapy in ER-positive, HER2-negative breast cancer. *Cancer Lett.* 2014; 355(1):70-75.
6. Filipits M, Rudas M, Jakesz R et al. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. *Clin Cancer Res.* 2011; 17(18):6012-6020.
7. Sestak I, Buus R, Cuzick J, et al. Comparison of the performance of 6 prognostic signatures for estrogen receptor-positive breast cancer: A secondary analysis of a randomized clinical trial. *JAMA Oncol.* 2018; 4(4):545-553.

Sincerely,



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