January 27, 2020

Submitted by:	Senior VP Medical Affairs
Name:	Royce T. (Terry) Adkins, M.D.
Company/Organization:	Myriad Genetics Laboratories, Inc.
Address:	320 Wakara Way, Salt Lake City, UT 84108
Phone:	801-883-3203
Email:	terry.adkins@myriad.com
NCCN Guidelines panel	Breast Cancer (treatment)

The NCCN Jan. 15, 2020 update states on BINV-N (3 of 4) under "Treatment Implications" that *"The [12-gene] 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[13]"*, indicating that the 12-gene EndoPredict assay can be used to predict chemo-benefit.

Specific Changes: Below we highlight discrepancies to the above statement in the guidelines and offer changes that will provide accuracy, clarity and consistency.

1. BINV-6: Decision tree states *"Strongly consider 21-gene RT-PCR assay (category 1)[kk,ll]"*
   a. We request the decision tree be modified for accuracy to state: *"Consider 21-gene RT-PCR assay (category 1); consider 12-gene RT-PCR assay (category 2A)[kk]".*
2. BINV-6: Footnote "kk" states *"Other prognostic gene expression assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy."*
   a. The change suggested in 1.a. describes the two tests with chemo-prediction and the kk footnote is accurate when the requested change is incorporated.
3. BINV-6: Describes the RS categories <26, 26-30, and ≥31 in the second bracket of the decision tree.
   a. We request that "EPclin Low (≤3.3)" be added under RS <26 and "EPclin High (>3.3)" be added under RS ≥31.
4. BINV-6: The footnote superscript of "jj" is incorrect in the decision tree.
   a. The footnote superscript "jj" should say "mm".
5. BINV-N (1 of 4): States *"No"* under the Predictive column for the 12-gene (EndoPredict) assay.
   a. We request it state "Yes" as the 12-gene assay is now included for chemo-prediction.

(cont. on next page)

6. BINV-N (3 of 4): In the row for the 12-gene assay it states *"Low (<3.33)"* and *"High (>3.33)"*
   a. We request this be changed to "EPclin Low (≤3.3)" and "EPclin High (>3.3)". The 12-gene test reports an EP molecular score *and* an EPclin score. It is important and accurate to clarify EPclin and to state "3.3" (not "3.33) and include "**≤**" and "**>**" in the correct locations.

7. BINV-N (1 of 4): Footnote "a" states *"…Other prognostic gene expression assays can provide additional prognostic information…but are unknown if predictive of chemotherapy benefit in 1-3 positive lymph nodes."*
   a. We request this statement be removed since when request "5.a." is incorporated, the table on BINV-N (1 of 4) will now accurately state prognosis and prediction ability for each assay.

8. BINV-7: Footnote "nn" states: "*Regarding the 21-gene RT-PCR assay, a secondary analysis of a prospective trial suggests that the test is predictive for women with 1-3 involved ipsilateral axillary lymph modes. Other gene expression assays have not been proven to be predictive of chemotherapy benefit."*
   a. We suggest changes (in red) to the footnote to acknowledge the new 12-gene chemo-prediction NCCN decision: *"Regarding the 21-gene RT-PCR assay, 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 RT-PCR assay, a multicohort prospective analysis of 3,746 archived tumors from chemoendocrine (GEICAM 2003-02/9906) and endocrine only cohorts (ABCSG 6/8, TransATAC) that included 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)[1]. Other multigene assays have not been shown to be predictive of chemotherapy benefit."*

References:

1. Sestak 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 176(3):377-386, 2019.

We feel the incorporation of these changes will provide the most clear and impartial description of the different multi-gene tests.

Sincerely,

Royce (Terry) Adkins, MD

Digitally signed by Royce (Terry) Adkins, MD
DN: cn=Royce (Terry) Adkins, MD, o=Myriad Genetics, ou=Myriad Women's Health, email=terry.adkins@myriad.com, c=US
Date: 2020.01.27 16:17:25 -07'00'

Royce (Terry) Adkins, MD
Senior VP Medical Affairs, Myriad Genetic Laboratories, Inc.