Submitted by: Chief Medical Officer **Date of Request**: July 23, 2019
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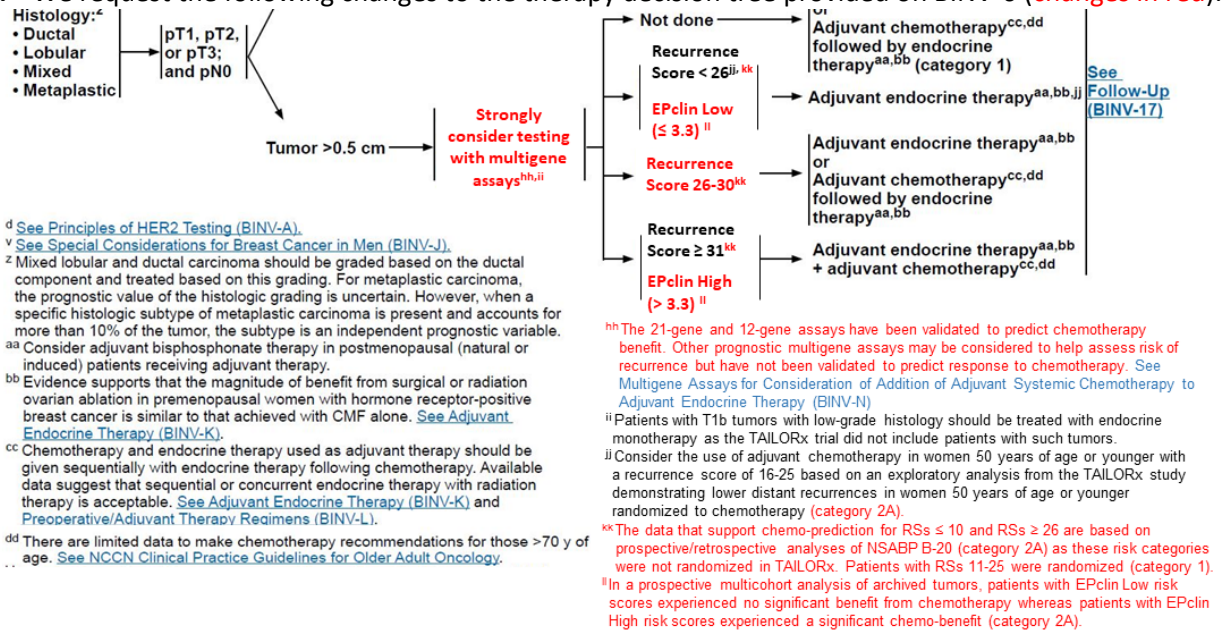
NCCN Guidelines Panel: Breast Cancer (Treatment)

Specific Changes:

1. We request the following changes to the therapy decision tree provided on BINV-6 (changes in red):



[d] See Principles of HER2 Testing (BINV-A).
[v] See Special Considerations for Breast Cancer in Men (BINV-J).
[z] Mixed lobular and ductal carcinoma should be graded based on the ductal component and treated based on this grading. For metaplastic carcinoma, the prognostic value of the histologic grading is uncertain. However, when a specific histologic subtype of metaplastic carcinoma is present and accounts for more than 10% of the tumor, the subtype is an independent prognostic variable.
[aa] Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant therapy.
[bb] Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. See Adjuvant Endocrine Therapy (BINV-K).
[cc] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable. See Adjuvant Endocrine Therapy (BINV-K) and Preoperative/Adjuvant Therapy Regimens (BINV-L).
[dd] There are limited data to make chemotherapy recommendations for those >70 y of age. See NCCN Clinical Practice Guidelines for Older Adult Oncology.

[hh] The 21-gene and 12-gene assays have been validated to predict chemotherapy benefit. Other prognostic multigene assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy. See Multigene Assays for Consideration of Addition of Adjuvant Systemic Chemotherapy to Adjuvant Endocrine Therapy (BINV-N)
[ii] Patients with T1b tumors with low-grade histology should be treated with endocrine monotherapy as the TAILORx trial did not include patients with such tumors.
[jj] Consider the use of adjuvant chemotherapy in women 50 years of age or younger with a recurrence score of 16-25 based on an exploratory analysis from the TAILORx study demonstrating lower distant recurrences in women 50 years of age or younger randomized to chemotherapy (category 2A).
[kk] The data that support chemo-prediction for RSs ≤ 10 and RSs ≥ 26 are based on prospective/retrospective analyses of NSABP B-20 (category 2A) as these risk categories were not randomized in TAILORx. Patients with RSs 11-25 were randomized (category 1).
[ll] In a prospective multicohort analysis of archived tumors, patients with EPclin Low risk scores experienced no significant benefit from chemotherapy whereas patients with EPclin High risk scores experienced a significant chemo-benefit (category 2A).

2. We request the following changes to the Multigene Assays Table on BINV-N (1of2):

a. Change "not determined" to "Yes" in the Predictive column for the 12-gene EndoPredict assay.
b. Change "Other" to "Preferred" in the NCCN Category of Preference column for the 12-gene EndoPredict assay.
c. Change "Low (<3.3287)" to "EPclin Low (≤ 3.3)" & "High (>3.3287)" to "EPclin High (> 3.3)" in Recurrence Risk column.
d. Incorporate the NCCN Category of Evidence and Consensus information into the Predictive and Prognostic columns for each assay; for EndoPredict, list "category 2A" under Predictive, and "category 1" under the Prognostic column.
e. Add the following text (in red) to the Treatment Implications column for EndoPredict:

"For patients with T1 and T2 hormone receptor-positive, HER2-negative and lymph node-negative tumors, a 12-gene EPclin Low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a-T1b, N0, M0.[7] In ABCSG 6/8, patients in the EPclin Low-risk group had risk of distant recurrence of 4% at 10 years and in the TransATAC study, patients with 1-3 positive nodes in the EPclin Low-risk group had a 5.6% risk of distant recurrence at 10 years.[1,7] The EPclin 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 (GEICAM 2003-02/9906) and endocrine only cohorts (ABCSG 6/8, TransATAC), that included women with lymph node-negative and lymph node-positive disease.[2] Patients with EPclin Low scores derived no benefit from the addition of chemotherapy to endocrine therapy, whereas those with EPclin High scores experienced significant chemo-benefit. A statistically significant interaction between EPclin score and treatment (p=0.022) was observed (Category 2A). Further, the chemo-predictive power of the 12-gene test is validated in a modeling study showing that women with EPclin Low risk scores had minimal differences in recurrence-free survival whether treated with or without chemotherapy, whereas women with EPclin High risk scores experienced significant chemotherapy benefit.[3]"

3. Add (in red) to Footnote "a" page BINV-N page 2of2:

"The 21-gene assay (Oncotype Dx) and the 12-gene assay (EndoPredict) are preferred by the NCCN Breast Cancer Panel for node negative breast cancer. Other prognostic multigene assays can provide additional prognostic information in patients with 1-3 positive lymph nodes. The prospective analysis of archived tumors that supports chemo-prediction for the 12-gene EndoPredict assay included 1,284 women with node positive disease. It is unknown if other multigene assays are predictive of chemotherapy benefit in 1-3 positive lymph nodes."

4. Remove citation 10 (Filipits) from the Treatment Implications for the "Oncotype Dx (for pN+ or node positive) row.

FDA Clearance: Not applicable.

Rationale for changes:

1. The EndoPredict 12-gene expression test is validated to predict response to chemotherapy in a prospective analysis of archived tumors from patients treated with chemo-endocrine therapy including taxanes (n=1,116) (GEICAM 2003-02/9906), and patients treated with endocrine therapy alone (n=2,630) (ABCSG-6/8 and TransATAC trials).[2] The multicohort analysis included 3,746 women, with ER+, HER2- disease and reported a statistically significant interaction between EPclin score and treatment (p=0.022). Patients with EPclin Low risk scores experienced minimal chemotherapy benefit whereas those with High risk scores experienced significant chemo-benefit that increased as the risk score increased. The predictive power of EndoPredict was further validated in a modeling study that shows that women with EPclin Low risk scores had minimal differences in recurrence-free survival whether treated with or without chemotherapy whereas women with EPclin High risk scores experienced significant chemotherapy benefit[3]. Similar to EndoPredict, the 21-gene assay that first received NCCN approval for chemo-prediction relied on data from a prospective/retrospective analysis for prediction of chemo-benefit (category 2A)[4]. After TAILORx, the 21-gene test still relies on data from the prospective/retrospective analysis of the NSABP-B20 trial to predict chemo-benefit in high risk and very low risk patients (ie. RSs ≥ 26 or RSs < 10) as these categories were not randomized in TAILORx.

2. Rationale for changes to the Multigene Assays Table:

a. EndoPredict is validated for chemo-prediction (see rationale for request 1, above).

b. The NCCN Categories of Preference describe Preferred as "Interventions that are based on superior efficacy, safety and evidence;" page MS-1. In two head-to-head analyses, EndoPredict has superior prognostic performance over other assays, including the 21-gene assay.[6,7] EndoPredict is validated for chemo-prediction with two studies[2,3].

c. EndoPredict reports EPclin Low risk (≤ 3.3) or EPclin High risk (> 3.3) results and risk scores to one decimal point.

d. The multigene tests have different levels of evidence for prognosis and prediction thus it is more appropriate to list the levels under the Prognosis and Prediction columns. We request that EndoPredict receive 'category 1' evidence for Prognosis: i) the test consistently identifies a group of patients that have a very low risk of distant recurrence at 10 years[1,7], ii) a recent secondary analysis of the TAILORx trial showed that the clinical risk factors of tumor size and grade significantly improve the prognostic ability of gene expression alone[5] and EndoPredict incorporates the clinical factors of tumor size and nodal status in its risk algorithm[1], and iii) in head-to-head comparisons, EPclin has superior prognostic performance to other tests, including the 21-gene assay.[6,7] We request to receive 'category 2A' evidence for Prediction as we provide two validation studies[2,3].

e. This is a provision of the data that supports the chemo-prediction validation claim.

3. The requested text change in the Footnote "a" to the Multigene Table on page BINV-N (2 of 2) is providing data support.

4. Citation 10 cites Filipits et al Clin Cancer Res 2011, describing development and validation of EndoPredict.

References:

[1]Filipits 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 7(18):6012-6020, 2011.

[2]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.

[3]Soliman et al. Predicting expected absolute chemotherapy treatment benefit in women with early stage-breast cancer using EndoPredict, an integrated 12-gene clinico-molecular assay. JCO Precis Oncol, accepted for publication, 2019.

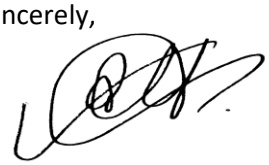
[4]Paik et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 24(23):3726-34, 2006.

[5]Sparano et al. Clinical and genomic risk to guide the use of adjuvant therapy for breast cancer. NEJM. 380(25):2395, 2019.

[6]Buus et al. Comparison of EndoPredict and EPclin with Oncotype Dx recurrence score for prediction of risk of distant recurrence after endocrine therapy. JNCI J Natl Cancer Inst 108(11):djw149, 2016.

[7]Sestak 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 4(4):545-553, 2018

Sincerely,



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