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 (<3.2827)” to “EPclin Low (≤ 3.3)” & “High (>3.2827)” 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. 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. 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 the GEICAM 2003/02/9906 and endocrine only cohorts (ABCSG 6/8, TransATAC), that included women with lymph node-negative and lymph node-positive disease. 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.”
   f. 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."
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). 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. 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). 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. EndoPredict is validated for chemo-prediction with two studies.
   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, 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 and EndoPredict incorporates the clinical factors of tumor size and nodal status in its risk algorithm, and iii) in head-to-head comparisons, EPclin has superior prognostic performance to other tests, including the 21-gene assay. We request to receive ‘category 2A’ evidence for Prediction as we provide two validation studies.
   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:


Sincerely,

Johnathan Lancaster, MD, PhD
Chief Medical Officer, Myriad Genetic Laboratories Inc.