NCCN Guidelines Panel: Breast Cancer

On behalf of Biotheranostics Inc., I respectfully request the NCCN Breast Cancer Panel to update the NCCN Guidelines based on the enclosed data for the Breast Cancer Index (BCI) in the evaluation of patients with hormone receptor-positive (HR+), HER2-negative early stage breast cancer to stratify patients by risk of late (post- 5 years from diagnosis) distant recurrence, and to identify patients for likelihood of benefit from extended endocrine therapy.

Specific Changes: Addition of a separate table in section BINV-M, similar in format to that previously added by the NCCN in 2018 for adjuvant chemotherapy decision-making, which summarizes validated multigene assays for extended adjuvant endocrine therapy decision-making.

MULTIGENE ASSAYS FOR CONSIDERATION OF EXTENSION OF ENDOCRINE THERAPY

<table>
<thead>
<tr>
<th>Assay</th>
<th>Predictive</th>
<th>Prognostic</th>
<th>NCCN Category of Preference</th>
<th>NCCN Category of Evidence and Consensus</th>
<th>Recurrence Risk/Likelihood of Extended Endocrine Benefit</th>
<th>Treatment Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-gene assay (Breast Cancer Index; BCI)</td>
<td>Yes (2 gene HoxB13/IL17R H/I Binary (High vs Low likelihood)</td>
<td>Yes (11 gene BCI score) – Individualized risk of late DR in years 5-10 post-diagnosis (High versus Low risk categories)</td>
<td></td>
<td></td>
<td></td>
<td>• Patients with HR+, HER2-negative, N0 tumors categorized by BCI Score as low risk for late distant recurrence (BCI Score &lt; 5.0825) had a mean distant recurrence risk of 2.5-3.5% in years 5 to 10 post diagnosis in three validation cohorts.1,2,3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
<td>• Patients with HR+, HER2-negative, N0/N+ tumors categorized by BCI as H/I Low did not significantly benefit from more than 5 years of endocrine therapy in the MA.17 and Trans-aTTom studies.4,5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Patients with HR+, HER2-negative, N0/N+ tumors categorized by BCI as H/I High showed significant benefit from more than 5 years of endocrine therapy in the MA.17 and Trans-aTTom studies.4,5 Relative risk reduction was 65% in both the MA.17 and Trans-aTTom studies.</td>
</tr>
</tbody>
</table>

* Residual risk of recurrence after completing primary adjuvant endocrine therapy

Regulatory Status: BCI testing is conducted, and the results are generated, at the Biotheranostics clinical laboratory in San Diego, California. The Biotheranostics clinical laboratory is Clinical Laboratory Improvement Amendments (CLIA)- certified, College of American Pathologists (CAP)-accredited, and licensed in all 50 states.

Rationale: With newly reported Trans-aTTom data, BCI strengthens its evidence level to 1B by Simon and Hayes criteria6 for prediction of response to extended endocrine therapy4,5 and prognosis of late distant...
recurrence\textsuperscript{1,2,3}, providing unique clinical utility to individualize selection and optimize the risk-to-benefit ratio for extended endocrine therapy in patients diagnosed with HR+ early stage breast cancer.

The following articles are submitted in support of the proposed changes:

5. Bartlett JM, et al. Trans-aTTom: Breast Cancer Index for prediction of endocrine benefit and late distant recurrence (DR) in patients with HR+ breast cancer treated in the adjuvant tamoxifen—To offer more? (aTTom) trial. Annals of Oncology (manuscript accepted for publication)

We appreciate the opportunity to provide this information for consideration by the NCCN Breast Cancer Guideline Panel. If you have any questions or require additional information, please do not hesitate to contact me directly (858-587-5884 or cathy.schnabel@biotheranostics.com).

Catherine Schnabel, PhD
Chief Scientific Officer
Biotheranostics, Inc.