**Table 2. Requirements for a Marker-Based Test to Reach Level IB Evidence of Clinical Utility on the Basis of Prospective-Throw Back Studies**

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Adequate data from archived specimens and patients suitable for analyses</td>
<td>High</td>
</tr>
<tr>
<td>2. The marker-based test should be analytically and preanalytically validated</td>
<td>Strong</td>
</tr>
<tr>
<td>3. The results from archived specimens should be validated by using specimens from one or more similar, but separate studies.</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

**Abbreviations**

- ER: estrogen receptor; PgR: progesterone receptor; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; IPMA: intranuclear phospho-MAPK; Ki67: proliferation index; LG: low grade; MT: microtubule; PI: phosphatase and tensin homolog; PPI: protein phosphatase 1, isotype 1; R1: strong recommendation; R2: moderate recommendation; RS: randomized study; S: strong; IB: intermediate; U: insufficient; E: evidence-based; I: informal consensus; H: high; L: low; |
Key Points

- In an era of great interest in personalized, precision medicine, the role of biomarker approaches to guide clinical care has taken on new and greater importance than in the past.
- In addition to estrogen and progesterone receptors and human epidermal growth factor receptor 2 (HER2), the panel found substantial evidence of clinical utility for the biomarker assays MammaPrint, Oncotype DX, EndoPredict, PAM50, Breast Cancer Index, and urokinase plasminogen activator and plasminogen activator inhibitor type 1 in subgroups of breast cancer patients.
- No biomarker except for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 was found to guide choices of specific treatment regimens.
- Treatment decisions should also consider disease stage, comorbidities, and patient preferences.

Diagnosis

- Patients with hormone receptor-positive breast cancer who have not received adjuvant systemic therapy should be evaluated for the presence of hormone receptor-negative (HR-negative) breast cancer.
- Patients with hormone receptor-positive breast cancer who have received adjuvant systemic therapy should undergo post-treatment endocrine therapy.
- Early-Stage Invasive Breast Cancer with Known ER/PgR and HER2 Status

- If a patient has HER2-positive breast cancer or triple negative (TN) breast cancer, the clinician may use the 12-gene risk score (EndoPredict; Sividon Diagnostics, Berlin, Germany) to guide decisions on adjuvant systemic chemotherapy. (Strong Recommendation; IC-Ins)
- If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should NOT use the MammaPrint assay to guide decisions on adjuvant systemic chemotherapy. (Strong Recommendation; IC-Ins)
- If a patient has ER/PgR-positive, HER2-negative, triple negative breast cancer, the clinician should NOT use the EndoPredict assay to guide decisions on adjuvant systemic chemotherapy. (Moderate Recommendation; EB-I)
- If a patient has ER/PgR-positive, HER2-negative, node-positive breast cancer, the clinician may use Oncotype DX to guide decisions on adjuvant systemic chemotherapy. (Strong Recommendation; IC-Ins)
- If a patient has HER2-positive breast cancer or TN breast cancer, or TN breast cancer and has had 5 years of endocrine therapy without evidence of disease, the clinician should NOT use immunohistochemistry 4 (IHC4) to guide decisions on adjuvant systemic therapy. (Weak Recommendation; EB-H)

Oncotype DX

- If a patient has HER2-positive breast cancer or HER2-negative breast cancer, the clinician may use the 21-gene recurrence score (RS; Oncotype DX; Genomic Health, Redwood City, CA) to guide decisions on adjuvant systemic chemotherapy. (Strong Recommendation; IC-Ins)
- If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should NOT use the Oncotype DX assay to guide decisions on adjuvant systemic chemotherapy. (Moderate Recommendation; EB-I)

MammaPrint

- If a patient has ER/PgR-positive, HER2-negative (node-negative) breast cancer, the clinician should use the MammaPrint assay to guide decisions regarding adjuvant systemic chemotherapy. (Moderate Recommendation; IC-L)

PAM50 Risk of Recurrence Score

- If a patient has ER/PgR-negative, HER2-negative (node-negative) breast cancer, the clinician may use the PAM50 risk of recurrence (ROR) score (PamQcast Breast Cancer Prognostic Gene Signature Assay; NonS零碎，Technologies，Seattle，WA) in conjunction with other clinicopathologic factors, to guide decisions on adjuvant systemic therapy. (Strong Recommendation; EB-I)

Key Points

- Immunohistochemistry 4 (IHC4)

- If a patient has HER2-positive (H2-positive or node-negative) breast cancer, the clinician should NOT use immunohistochemistry 4 (IHC4) to guide decisions on adjuvant systemic chemotherapy. (Moderate Recommendation; EB-I)
- If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should NOT use IHC4 to guide decisions on adjuvant systemic therapy. (Strong Recommendation; IC-C)

Circulating Tumor Cells

- The clinician should not use circulating tumor cells to guide decisions on adjuvant systemic therapy. (Strong Recommendation; IC-C)
- The clinician should not use circulating tumor cells to guide decisions on extended endocrine therapy. (Strong Recommendation; IC-C)

Urokinase Plasminogen Activator and Plasminogen Activator Inhibitor Type 1

- If a patient has ER/PgR-positive, HER2-negative (node-negative) breast cancer, the clinician may use urokinase plasminogen activator and plasminogen activator inhibitor type 1 to guide decisions on adjuvant systemic therapy. (Weak Recommendation; EB-I)

Tumor-Infiltrating Lymphocytes

- If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should NOT use tumor infiltrating lymphocytes to guide decisions on adjuvant systemic therapy. (Strong Recommendation; IC-C)

- If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should NOT use tumor infiltrating lymphocytes to guide decisions on extended endocrine therapy. (Strong Recommendation; IC-C)

- Protein encoded by the MKI67 gene labeling index by IHC should NOT be used to guide choice on adjuvant chemotherapy. (Moderate Recommendation; EB-I)

Extended Endocrine Therapy

- If a patient has HER2-positive breast cancer or HER2-negative breast cancer and has 5 years of endocrine therapy without evidence of disease, the clinician should NOT use circulating tumor cells to guide decisions on extended endocrine therapy. (Moderate Recommendation; EB-I)

For patients who present with a hormone receptor-positive, HER2-negative breast cancer and have not received adjuvant systemic therapy:

- If a patient older than 50 and whose tumors have Oncotype DX recurrence scores ≥25, and for patients ≤50 whose tumors have Oncotype DX recurrence scores >20, the clinician may use Oncotype DX assay to guide decisions on adjuvant systemic chemotherapy. Care may offer endocrine therapy alone. (Strong Recommendation; EB-I)
- For patients 40 years of age or younger with Oncotype DX recurrence scores ≥36 to 15, clinicians may offer chemotherapeutic regimens. (Strong Recommendation; EB-I)
- Patients with Oncotype DX recurrence scores >30 should be considered candidates for chemotherapeutic therapy. (Strong Recommendation; EB-I)

For patients who present with hormone receptor-positive, HER2-negative breast cancer and have received adjuvant systemic therapy:

- If a patient has ER/PgR and HER2-negative, node-positive breast cancer, the clinician should use the Estrogen Receptor (ER), Progesterone Receptor (PgR), and HER2 status to guide decisions on extended endocrine therapy. (Strong Recommendation; IC-Ins)
- If a patient has ER/PgR- and HER2-negative, breast cancer, the clinician should use the 70-gene recurrence risk score (MammaPrint; Amsterdam, Netherlands) to guide decisions on extended endocrine therapy. (Strong Recommendation; EB-I)
- If a patient has ER/PgR- and HER2-negative, breast cancer, the clinician should use the Oncotype DX assay to guide decisions on extended endocrine therapy. (Strong Recommendation; IC-Ins)
- If a patient has ER/PgR-positive, HER2-negative (node-positive) breast cancer, the clinician should use the PAM50 ROR score to guide decisions on adjuvant systemic therapy. (Strong Recommendation; EB-I)
- If a patient has ER/PgR-positive, HER2-negative (node-negative) breast cancer, the clinician may use the PAM50 ROR score to guide decisions on adjuvant systemic therapy. (Strong Recommendation; EB-I)
- If a patient has ER/PgR-negative, HER2-negative (node-negative) breast cancer, the clinician should use the Breast Cancer Index to guide decisions on extended endocrine therapy. (Moderate Recommendation; IC-I)
- If a patient has TN breast cancer, the clinician should NOT use the PAM50 ROR score to guide decisions on adjuvant systemic therapy. (Strong Recommendation; EB-I)
- If a patient has ER/PgR-positive, HER2-negative (node-negative) breast cancer, the clinician should use the Breast Cancer Index to guide decisions on adjuvant systemic therapy. (Moderate Recommendation; EB-I)
- If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should NOT use the MammaPrint assay to guide decisions on adjuvant systemic chemotherapy. (Strong Recommendation; IC-Ins)
- If a patient has ER/PgR-positive, HER2-negative (node-negative) breast cancer, the clinician should NOT use the five-gene assay (MammaPrint; Amsterdam, Netherlands) to guide decisions on extended endocrine therapy. (Strong Recommendation; IC-C)
- If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should NOT use the five-gene assay (MammaPrint; Amsterdam, Netherlands) to guide decisions on extended endocrine therapy. (Strong Recommendation; IC-C)