Table 1. Breast Cancer Biomarkers to Guide Adjuvant Therapy

Test	ER/PgR-positive, HER2-negative (node-negative)	ER/PgR-positive, HER2-negative (node-positive)	HER2-positive or TN
Oncotype DX	Yes	No	No
Endopredict	Yes	No	No
MammaPrint	Yes[a]	Yes[b]	No
Pam50	Yes	No	No
Mammostrat	No	No	No
Breast Cancer Index	Yes	No	No
IHC4	No	No	No
Urokinase plasminogen activator and plasminogen activator inhibitor type 1	Yes	–	No
Circulating Tumor Cells	No	No	No
Tumor-Infiltrating Lymphocytes	No	No	No
Protein Encoded Mk167 Gene	No	No	No

[a] In patients with high clinical risk per MINDACT categorization.
[b] In patients with 1–3 positive nodes and high clinical risk per MINDACT categorization.

Additional Biomarkers to Guide Specific Drug/Regimen Choice

Tamoxifen

- **The clinician should *NOT* use CYP2D6 polymorphisms to guide adjuvant endocrine therapy selection. (Moderate Recommendation; EB-I)**
- **The clinician should *NOT* use p27 expression by IHC to guide adjuvant endocrine therapy selection. (Strong Recommendation; IC-L)**

Aromatase Inhibitors

- **The clinician should *NOT* use protein encoded by the MKI67 gene labeling index by IHC to guide adjuvant endocrine therapy selection. (Moderate Recommendation; EB-I)**

Taxanes

- **The clinician should *NOT* use microtubule-associated protein Tau mRNA expression or mRNA expression by IHC to guide adjuvant chemotherapy selection. (Moderate Recommendation; EB-I)**
- **The clinician should *NOT* use HER1/epidermal growth factor receptor expression by IHC to guide adjuvant chemotherapy selection. (Moderate Recommendation; EB-L)**

Anthracyclines

- **The clinician should *NOT* use TOP2A gene amplification or TOP2A protein expression by IHC to guide adjuvant chemotherapy selection. (Moderate Recommendation; EB-H)**
- **The clinician should *NOT* use HER2 and TOP2A gene coamplification; CEP17 duplication; or TIMP-1, FOXP3, or p53 to guide adjuvant chemotherapy selection. (Moderate Recommendation; EB-I)**

Trastuzumab

- **If a patient has HER2-positive breast cancer, the clinician should *NOT* use phosphatase and tensin homolog (PTEN) to guide adjuvant therapy selection. (Moderate Recommendation; EB-I)**
- **If a patient has HER2-positive breast cancer, the clinician should *NOT* use soluble HER2 levels to guide selection of type of adjuvant therapy. (Moderate Recommendation; EB-L)**

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

Requirements
1. Adequate amounts of archived specimen must be available from enough patients from a prospective trial (which for predictive factors should generally be a randomized design) for analyses to have adequate statistical power and for the patients included in the evaluation to be clearly representative of the patients in the trial.
2. The marker-based test should be analytically and preanalytically validated for use with archived specimens.
3. The plan for marker evaluation should be completely specified in writing before the performance of marker assays on archived specimens and should be focused on the evaluation of a completely defined marker-based test.
4. The results from archived specimens should be validated by using specimens from one or more similar, but separate studies.

NOTE. Adapted from Simon et al. *J Natl Cancer Inst.* 2009;101:1446-1452.

Recommendation Grading

Type		Evidence Quality		Strength of Recommendation
EB	Evidence-based	H	High	Strong
IC	Informal consensus	I	Intermediate	Moderate
		L	Low	Weak
		Ins	Insufficient	

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

Additional information, which may include data supplements, slide sets, patient versions, and other clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines

Abbreviations

ER, estrogen receptor; **HER2**, human epidermal growth factor receptor 2; **IHC**, immunohistochemistry; **PR**, progesterone receptor; **PTEN**, phosphatase and tensin homolog; **RS**, recurrence score; **TN**, triple negative

Source

Andre F et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* 2019 May xx; doi: xx.xxxx/JCO.2019.xx.xxxx

Krop I et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: Focused Update of 2016 American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2017 Aug 20;35(24):2838-2847.

Harris LN et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2016 Apr 1;34(10):1134-50.

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AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Breast Cancer Biomarkers

To Guide Systemic Therapy in Early Disease

Adapted from:
Andre F et al. *J Clin Oncol.* 2019
Krop I et al. *J Clin Oncol.* 2017 Aug 20;35(24):2838-2847
Harris LN et al. *J Clin Oncol.* 2016 Apr 1;34(10):1134-50

Key Points

Diagnosis

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Key Points

- In an era of great interest in personalized, precision medicine, the role of tumor biomarker assays in guiding clinical care has taken on even greater importance than in the past.
- In addition to estrogen and progesterone receptors and human epidermal growth factor receptor 2 (HER2), the panel found sufficient 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 specific subgroups of breast cancer.
- 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

For patients who present with a hormone receptor positive, HER2 not overexpressed, axillary node negative early breast cancer:

- For patients older than 50 and whose tumors have Oncotype DX recurrence scores <26, and for patients ≤50 whose tumors have Oncotype DX recurrence scores <16, there is little to no benefit from chemotherapy. Clinicians may offer endocrine therapy alone. (Strong Recommendation; EB-H)
- For patients 50 years of age or younger with Oncotype DX recurrence scores of 16 to 25, clinicians may offer chemoendocrine therapy. (Moderate Recommendation; EB-I)
- Patients with Oncotype DX recurrence scores >30 should be considered candidates for chemoendocrine therapy. (Strong Recommendation; EB-H)
- Based on Expert Panel consensus, oncologists may offer chemoendocrine therapy to patients with Oncotype DX scores of 26 to 30. (Moderate Recommendation; IC-Ins)

Early-Stage Invasive Breast Cancer with Known ER/PgR and HER2 Status

Oncotype DX

- If a patient has ER/PgR-positive, HER2-negative (node-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; EB-H)
- If a patient has ER/PgR-positive, HER2-negative (node-positive) breast cancer, the clinician should ***NOT*** use the 21-gene RS to guide decisions on adjuvant systemic chemotherapy. (Moderate Recommendation; EB-I)
- If a patient has HER2-positive breast cancer or triple negative (TN) breast cancer, the clinician should ***NOT*** use the 21-gene triple negative (RS) to guide decisions on adjuvant systemic therapy. (Strong Recommendation; IC-Ins)

Endopredict

- If a patient has ER/PgR-positive, HER2-negative (node-negative) breast cancer, the clinician may use the 12-gene risk score (EndoPredict; Sividon Diagnostics, Köln, Germany) 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 should ***NOT*** use the 12-gene risk score (EndoPredict) to guide decisions on adjuvant systemic chemotherapy. (Moderate Recommendation; EB-Ins)
- If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should ***NOT*** use the 12-gene risk score (EndoPredict) to guide decisions on adjuvant systemic therapy. (Strong Recommendation; IC-Ins)

MammaPrint

- If a patient has ER/PgR-positive, HER2-negative, node-negative, breast cancer, the MammaPrint assay (MammaPrint; Agendia, Irvine, CA) may be used in those with high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit. (Strong Recommendation; EB-H)
- If a patient has ER/PgR-positive, HER2-negative, node-negative, breast cancer, the MammaPrint assay should ***NOT*** be used in those with low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy since women in the low clinical risk category had excellent outcomes and did not appear to benefit from chemotherapy even with a genomic high risk cancer. (Strong Recommendation; EB-H)
- If a patient has ER/PgR-positive, HER2-negative, node-positive, breast cancer, the MammaPrint assay may be used in patients with 1-3 positive nodes and at high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit. (Moderate Recommendation; EB-H)
  - However, such patients should be informed that a benefit of chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node.
- If a patient has ER/PgR-positive, HER2-negative, node-positive, breast cancer, the MammaPrint assay should ***NOT*** be used in patients with 1-3 positive nodes and at low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy. There are insufficient data on the clinical utility of MammaPrint in this specific patient population. (Moderate Recommendation; IC-L)
- If a patient has HER2-positive breast cancer, the clinician should ***NOT*** use the MammaPrint assay to guide decisions regarding adjuvant systemic therapy. (Moderate Recommendation; IC-L)
  - Additional studies are required to address the role of MammaPrint in patients with this tumor subtype who are also receiving HER2-targeted therapy.
- If a patient has ER/PgR negative and HER2-negative breast cancer (triple negative), the clinician should ***NOT*** use the MammaPrint assay to guide decisions about adjuvant systemic chemotherapy. (Strong Recommendation; IC-Ins)

PAM50 Risk of Recurrence Score

- If a patient has ER/PgR-positive, HER2-negative (node-negative) breast cancer, the clinician may use the PAM50 risk of recurrence (ROR) score (Prosigna Breast Cancer Prognostic Gene Signature Assay; NanoString Technologies, Seattle, WA), in conjunction with other clinicopathologic variables, to guide decisions on adjuvant systemic therapy. (Strong Recommendation; EB-H)
- If a patient has ER/PgR-positive, HER2-negative (node-positive) breast cancer, the clinician should ***NOT*** use the PAM50-ROR to guide decisions on adjuvant systemic therapy. (Moderate Recommendation; EB-I)
- If a patient has HER2-positive breast cancer, the clinician should ***NOT*** use the PAM50-ROR to guide decisions on adjuvant systemic therapy. (Strong Recommendation; IC-Ins)
- If a patient has TN breast cancer, the clinician should ***NOT*** use the PAM50-ROR to guide decisions on adjuvant systemic therapy. (Strong Recommendation; IC-Ins)

Breast Cancer Index

- If a patient has ER/PgR-positive, HER2-negative (node-negative) breast cancer, the clinician may use the Breast Cancer Index to guide decisions on adjuvant systemic therapy. (Moderate Recommendation; EB-I)
- If a patient has ER/PgR-positive, HER2-negative (node-positive) breast cancer, the clinician should ***NOT*** use the Breast Cancer Index to guide decisions on adjuvant systemic therapy. (Strong Recommendation; IC-Ins)
- If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should ***NOT*** use the Breast Cancer Index to guide decisions on adjuvant systemic therapy. (Strong Recommendation;IC-Ins)

Mammostrat

- If a patient has ER/PgR-positive, HER2-negative (node-positive or node-negative) breast cancer, the clinician should ***NOT*** use the five-protein assay (Mammostrat; Clarient, a GE Healthcare company, Aliso Viejo, CA) 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 five-protein assay (Mammostrat) to guide decisions on adjuvant systemic therapy. (Strong Recommendation;IC-Ins)

Immunohistochemistry 4 (IHC4)

- If a patient has ER/PgR-positive, HER2-negative (node-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-Ins)

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-H)
- If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should ***NOT*** use urokinase plasminogen activator and plasminogen activator inhibitor type 1 to guide decisions on adjuvant systemic therapy. (Weak Recommendation; IC-Ins)

Circulating Tumor Cells

- The clinician should ***NOT*** use circulating tumor cells to guide decisions on adjuvant systemic therapy. (Strong Recommendation; EB-I)

Tumor-Infiltrating Lymphocytes

- If a patient has ER/PgR-positive, HER2-negative (node-positive or node-negative) breast cancer, the clinician should ***NOT*** use tumor infiltrating lymphocytes to guide decisions on adjuvant systemic therapy. (Strong Recommendation; IC-Ins)
- 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; EB-I)

Protein Encoded By The MKI67 Gene

- 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 ER/PgR-positive, HER2-negative (node-negative) breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, the clinician should ***NOT*** use multiparameter gene expression or protein assays (Oncotype DX, EndoPredict, PAM50, Breast Cancer Index, or IHC4) to guide decisions on extended endocrine therapy. (Moderate Recommendation; EB-I)