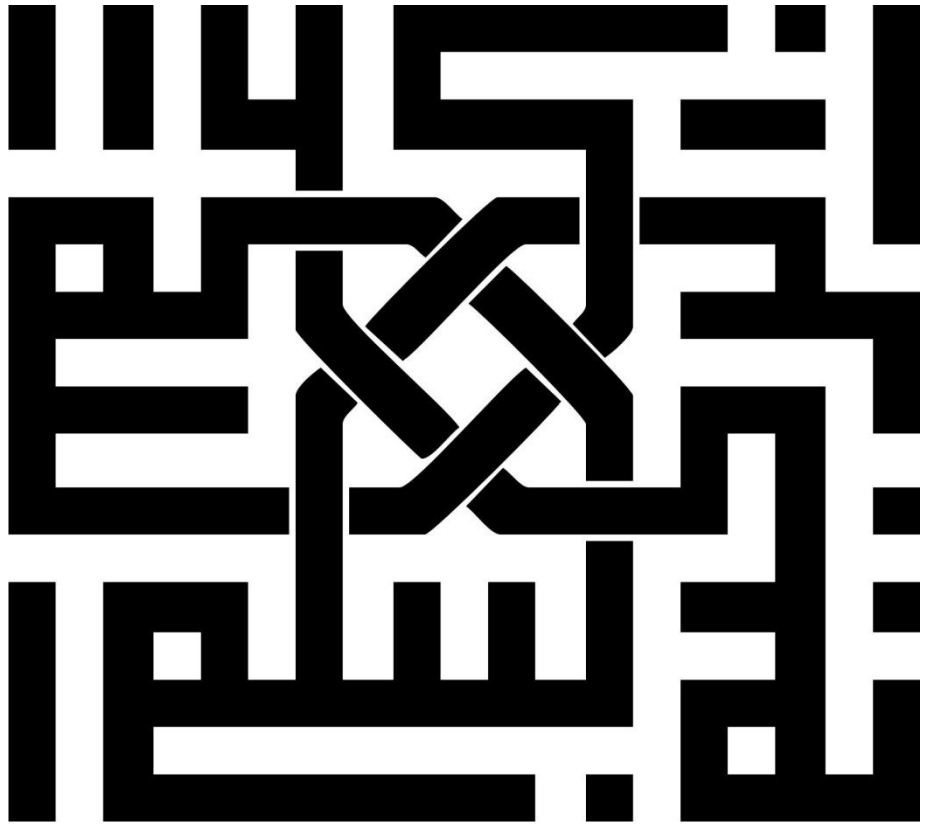

Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update

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biomarker Definition

The general biologic or molecular condition that distinguishes one patient group from another

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Criteria for evidence

- Analytic Validity:
  - Analytic validity refers to the accuracy, reliability, and reproducibility of the assay as demonstrated by preanalytic, technical, and scoring or interpretation methods
- Clinical Validity:
  - The ability of a tumor biomarker test to divide one population into two or more groups that differ either biologically or clinically
- Clinical Utility:
  - If use of the test is associated with a favorable balance of benefits to harms compared with treatment of the patient in the absence of the biomarker test result

Oncotype DX

- **Description**: a quantification tool for likelihood of breast cancer recurrence within 10 years of newly diagnosed, stage I or II, lymph node-negative, hormone receptor-positive breast cancer in women who will be treated with Endocrine therapy
- **Purpose**: Prognosis, recurrence, and therapeutic management
- **Specimen**: Paraffin-preserved tissue
- **Methodology**: RT-qPCR of 21 genes (5 control genes)
- **FDA approved**: No
- **Included in NCCN and ASCO**: Yes

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MammaPrint

- **Description**: 70-gene profile that classifies breast cancer into Low Risk or High Risk of recurrence, by measuring genes representative of all the pathways of cancer metastases which were selected for their predictive relationship to 10-year recurrence probability. MammaPrint is indicated for women who have stage I or II breast cancer, are lymph node positive or negative, are ER-positive or negative and tumor size of less than five centimeters.
- **Purpose**: Prognosis, recurrence, predictive, and therapeutic management of breast cancer
- **Specimen**: Formalin fixed, paraffin-embedded, fresh or frozen breast tumor tissue
- **Methodology**: Genomic signature by microarray-based RNA gene expression
- **Clinical Uses**: MammaPrint determines if the patient is a candidate for chemotherapy.
- **FDA approved**: Yes

EndoPredict assay

- **Description:**
  - stratifies patients with ER+ cancer into a low or high risk of recurrence if treated with adjuvant endocrine therapy alone
  - Epclin: Endopredict combined with nodal status and tumor size to compute a comprehensive risk score termed EPclin. The performance of EPclin was validated in two randomized phase III trials.
  - EndoPredict also identifies ER-positive patients who are at risk for late recurrence.
- **Purpose:** The assay is marketed in Europe as a diagnostic kit
- **Specimen:** Formalin fixed paraffin-embedded
- **Methodology:** RT-PCR-based assay of **8** cancer genes and **3** housekeeping control genes
- **FDA approved:** No but NICE (The National Institute for Health and Care Excellence) approved

PAM50 breast Intrinsic Classifier

- **Description**: examining 50 genes and sorts breast cancer into four subtypes. Each subtype responds differently to standard therapies, and knowing the subtype allows doctors to tailor treatment for each patient.
- **Purpose**: Prognostic and therapeutic management
- **Specimen**: Tumor tissue
- **Methodology**: RT-qPCR
- **Clinical Uses**: PAM50 assay can aid profiling for both prognosis and prediction of benefit from adjuvant tamoxifen and has been found superior to immunohistochemistry.
- **FDA approved**: No

Ki 67

IHC4 assay

- **Description:** It is based on a multivariate model that uses semi quantitative information from immunohistochemical assessment of ER, PR, HER2 and Ki67.
- **Purpose:** Therapeutic management, risk score for recurrence is calculated by an algorithm
- **Specimen:** Formalin fixed paraffin-embedded
- **Methodology:** immunohistochemical assessment of ER, PR, HER2 and Ki67.
- **Clinical Uses:** it uses information from ER, PR and Ki67 differently to how these markers are currently interpreted in routine practice. Physicians tend to use these markers as binary categories (that is, ER-positive vs. ER-negative, Ki67 low vs. Ki67 high, and so forth) and create distinct groups (with four binary markers, 16 different marker groups are possible); in contrast, IHC4 uses a mathematical formula that weighs the semi quantitative expression values and combines these into a single risk score.
- **FDA approved**: No

4. Breast cancer index

- **Description**: a prognostic biomarker that provides quantitative assessment of the likelihood of distant recurrence in patients diagnosed with estrogen receptor-positive, lymph node-negative breast cancer. In development and validation studies, BCI stratified ~50% of tamoxifen treated ER+, node-negative breast cancer patients into a low risk group for 10-year distant recurrence.
- **Purpose**: Prognostic and Recurrence
- **Specimen**: Formalin-fixed, paraffin-embedded (FFPE) tissue block
- **Methodology**: BCI is a molecular assay developed from the combination of two indices: HOXB13:IL17BR and Five cell cycle-associate gene index that assesses tumour grade.
- **FDA approved**: No

5. Circulating tumor cells

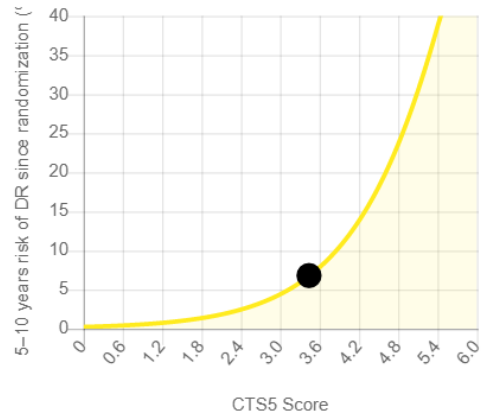
- The clinician should not use circulating tumor cells to guide decisions on adjuvant systemic therapy.
  - Type: evidence based
  - Evidence quality: intermediate
  - Strength of recommendation: strong

Clinical Treatment Score Post 5-years (CTS-5)

CTS⑤ CALCULATOR

Tumour size (mm)	20
Tumour Grade	Grade 1
Patient age (years)	45
Number of nodes involved	2

UPDATE RESULT ⇨



CTS5 SCORE	5–10 YEAR RISK	CTS5 RISK GROUP
3.44	6.8%	Intermediate

Tumor Infiltrating Lymphocytes

- Tumor infiltrating lymphocytes (TILs) has been observed mostly in a number of presented breast cancer cases.
- The developing forms of cancers that have a negative status enlargement of the axillary lymph nodes characteristic to a relatively small size of tumor and usually low grade ones are studied by use of TILs.
- Tumor infiltrating lymphocytes have a negative correlation with the age of a patient
- their count is positively associated with the survival period of the affected patients with the presence or absence of estrogen receptors.
- TILs are the predictive and potential prognostic markers in breast cancer.
- When a local relatively developed breast cancer is treated with neoadjuvant chemotherapy, any occurrence of tumor infiltrates of lymphocytes is an evident predictor of the response.

PDL-1

- PD-1 (CD279) is an inhibitory coreceptor which is expressed on the surface of T cells
- The activation of this PD-1 through binding of the ligand PD-L1 (B7-H1; CD274), which can be expressed on some immune cells (lymphocytes, dendritic cells, macrophages, and granulocytes), leads to the inhibition of the T cell response, to self-tolerance and immune tolerance
- physiologically, the PD-1/PD-L1 axis protects us from excessive immune responses and autoimmune reactions
- Many solid, and also some hematopoietic, neoplasms express PD-L1 to inactivate the T cell response, thereby bypassing this immune checkpoint and the response of our immune system to neoplastic cells
- This mechanism is also known as immune escape or local suppression of the immune system.
- Therapeutic monoclonal antibodies, so-called ICI (Immune Checkpoint inhibitors) , against PD-1 or PD-L1, can, however, suspend this inhibitory effect of the PD-1/ PD-L1 axis with T cells and the endogenous antitumoral immune response is thus reactivated