



Breast Cancer Testing

StrataFLEX and Breast Cancer Management

Management of breast cancer requires a rational approach to reduce treatment costs, provide effective chemotherapy and predict and prolong survival times.

To move clinicians easily through the testing process, Molecular Pathology Laboratory Network, Inc. (MPLN) offers StrataFLEX, an innovative health management strategy that provides patient-specific reflex testing options in a timely, cost-effective manner.

Evidence Based Laboratory Medicine

Evaluation of a patient's clinical and molecular expression provides valuable information when selecting appropriate treatment. Effective therapy is dependent on stage and type of breast cancer as determined by standard histologic features, tumor phenotype by immunohistochemistry and genotypic characteristics such as presence of hormone receptors and HER2 status.

Adjuvant chemotherapy is selected based on assessment of prognostic and predictive markers. Prognostic markers identify invasive cancers that will have good outcomes and low risk of metastases after surgery, whereas predictive markers identify patients who will benefit from a treatment regimen that provides improved recurrence-free disease and overall survival.

Hormone receptors and HER2 status define four intrinsic subtypes of breast cancer and outcomes.

Prognostic and Predictive Markers

| Subtypes | ER | PR | HER2 | Outcome |
|------------|-----|---------|------|---|
| Luminal A | Pos | Pos | Neg | Best prognosis Less aggressive/ hormone responsive |
| Luminal B | Pos | Neg/Pos | Pos | More aggressive/poorer prognosis |
| ERBB2 | Neg | Neg | Pos | Highly aggressive |
| Basal-Like | Neg | Neg | Neg | CK5/6+, EGFR+, ckit+ Aggressive/ higher risk of metastases |



MPLN

ONE SOURCE FOR LABORATORY TESTING

Make the right move.

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Molecular Pathology and Diagnostics

Diagnosis

Immunohistochemistry markers:

- Estrogen/Progesterone (ER/PR) receptors
- Invasive profile: CK5, p63, CK8/18
- Basal phenotype: cytokeratin (CK5, CK5/8, CK14, CK17), EGFR, p63
- Ductal / lobular: E-cadherin, CK 34BE12
- Undifferentiated: GCDFP15, Androgen receptor
- Adenocarcinoma: cytokeratins 8/18, BER-EP4
- Germ cell: PLAP
- Epithelial: Cytokeratins, SMA
- Apoptosis: Survivin

Prognosis

Immunohistochemistry markers:

- Prognostic profile: ER/PR receptors, HER2 and Ki67
- P53
- EGFR1(HER1)
- BCL2
- Cathepsin D

HER2/*neu* by fluorescence *in-situ* hybridization probes

Ploidy and S phase by flow cytometry

CellSearch circulating tumor cell (CTC) test

Serum HER2/*neu*

Targeted Drug Therapy

Tamoxifen: ER/PR receptor status

Tamoxifen/adjuvant: Invasive profile: CK5, p63, CK8/18

Herceptin® / HER2 amplification

Surveillance/Therapeutic Monitoring

CellSearch CTC test

Serum carcinoembryonic antigen (CEA)

Serum CA 15-3

Serum CA 27-29



ER/PR receptor status and P53 mutation

p53 is one of the most common mutated genes in carcinomas. 10-20% of primary breast cancers have over expression associated with aggressive disease and worse overall survival.

Receptor (estrogen and progesterone) status and p53 mutation assessment are commonly used to determine drug resistance and drug toxicity. Patients with p53 mutations show increased resistance to ionizing radiation.¹ Patients on adjuvant chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil benefit significantly compared to patients without the p53 mutation.^{2,3}

Ki67 by IHC

Ki67 is found in growing, dividing cells but is absent in the resting phase of cell growth. Studies indicate that high levels of Ki67 typically result in an aggressive tumor, a poor prognosis and a higher than average risk of recurrence.

Cell Cycle Analysis and DNA Ploidy

Studies show correlation between DNA ploidy, S-phase proliferation and tumor progression in breast cancer. DNA ploidy and cell cycle analysis utilizing flow cytometry is a rapid and efficient way to evaluate DNA content and proliferative activity (cell cycle/S-phase fraction) of cells.

HER2/*neu* by FISH and IHC

HER2 plays a key role in the regulation of overall cell growth and in 25-30% of patients with breast cancer. Studies show that HER2 amplification, as demonstrated by FISH, is a significant independent predictor of tumor recurrence. Patients with HER2 over expression on the surface of breast cancer cells may be candidates for antibody therapy Herceptin (Trastuzumab).

Invasive Profile (CK5, p63, CK8/18)

This (IHC) profile includes cytokeratin markers CK5 and CK8/18 as well as p63. The double staining cocktail highlights normal basal layers (epithelial layer) and tumors that may be micro-invading through the duct epithelium – thus changing the diagnosis from Ductal In-Situ and treatment with Tamoxifen to Invasive Ductal carcinoma with Tamoxifen treatment plus adjuvant therapy.

CellSearch Circulating Tumor Cell Test

The CellSearch™ System identifies and counts circulating tumor cells (CTCs) in a single blood sample. Results and serial testing of CTCs, in conjunction with other clinical methods for disease monitoring, assist physicians in predicting progression-free survival (PFS) and overall survival in patients with metastatic breast cancer (OS).^{8,9}

Tumor Markers

Tumor marker levels are used to monitor therapy response and disease progression. Decreasing levels of CA 15-3 and CEA are associated with a positive response to therapy; while increasing levels of CA 15-3 and CEA indicate disease progression. CA 15-3 and CA 27-29 have shown improved sensitivity and specificity over the use of CEA.^{4,5} While an elevated level of CEA is found in 64% of patients with metastatic disease, normal levels are found in 88% of patients without recurrent disease.^{6,7}

References

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