

PAM50 Breast Cancer Intrinsic Classifier

FOR DETERMINING BREAST CANCER SUBTYPE AND OTHER TUMOR CHARACTERISTICS THAT ARE USEFUL FOR PATIENT MANAGEMENT

Clinical Background

- Breast cancer is the most commonly diagnosed carcinoma among American women and the second-leading cause of cancer-related death.¹
- Approximately 190,000 women in the United States are diagnosed with breast cancer each year, and over 40,000 die from the disease.
- Early diagnosis and tailored therapies can significantly affect overall survival.
- Immunohistochemistry (IHC) staining for ER, PR, and HER2/*neu* (HER2) is the standard methodology for making a molecular diagnosis and determining treatment.
- Gene-expression profiling of breast cancer can identify different biologic subtypes (i.e., Luminal A, Luminal B, HER2-enriched, and Basal-like) that correspond to differences in patient outcome.^{2,3}
- Efficacy of adjuvant and neo-adjuvant drug regimens has been shown to vary among subtypes.^{2,3}

Indications for Ordering

The PAM50 Breast Cancer Intrinsic Classifier test is recommended for all patients diagnosed with invasive breast cancer, regardless of stage or ER status.

Pathophysiology

- The distribution of breast cancer subtypes varies in the population:
 - Luminal A: 35–40 percent
 - Luminal B: 25–30 percent
 - HER2-enriched 10–20 percent
 - Basal-like: 10–20 percent
- Luminal A tumors usually have intermediate to high expression of *ESR1* and estrogen-regulated genes and rarely have high *ERBB2* expression.
- Luminal B tumors usually have intermediate to high expression of *ESR1* and estrogen-regulated genes and often have higher proliferation than Luminal A tumors.
- HER2-enriched tumors usually have intermediate to high expression of *ERBB2* and intermediate to low expression of *ESR1* and estrogen-regulated genes. Approximately one-third of tumors subtyped as HER2-enriched are not HER2+ by immunohistochemistry (2+ or 3+ HER2 score) or fluorescence in-situ hybridization (DNA amplified for *ERBB2*).
- Basal-like tumors usually have low expression of *ESR1*, *PGR*, *ERBB2*, and estrogen-regulated genes, but have high proliferation.

Methodology

- RNA is extracted from formalin-fixed, paraffin-embedded tissue and converted to cDNA using both random and gene-specific primers.
- RT-qPCR is then performed on 50 classifier genes and five control genes simultaneously in a plate pre-manufactured at ARUP to determine RNA expression levels.
- Subtype predictions are done using a previously reported centroid-based algorithm.^{2,3}

Interpretation

- The subtype assignment corresponds to the overall tumor biology as characterized by the expression of 50 classifier genes and normalized to five control genes.^{2,3}
- Quantitative gene expression scores and subtype classification should be interpreted together.
- The gene expression scores provide an objective and quantitative method for measuring standard biomarkers used in breast cancer (e.g., *ESR1*/ER, *PGR*/PR, *ERBB2*/HER2).

Limitations

- This test should not be used as the sole means of diagnosis for patient management.
- The test is intended only for invasive breast cancer.
- The specimen must contain at least 75 percent breast cancer.

References

1. Centers for Disease Control and Prevention, National Program of Cancer Registries. <http://apps.nccd.cdc.gov/uscs/> (accessed on November 5, 2010).
2. Parker JS, et al. Supervised risk predictor of breast cancer based on intrinsic subtypes. *J Clin Oncol* 2009;27(8):1160–7.
3. Nielsen TO, et al. A comparison of PAM50 intrinsic subtyping with immunohistochemistry and clinical prognostic factors in tamoxifen-treated estrogen receptor positive breast cancer. *Clin Cancer Res* 2010;16(21):5222–32.

Test Information

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PAM50 Breast Cancer Intrinsic Classifier

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.