Molecular Diagnostic Testing in Breast Cancer

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Objectives: *An overview of molecular tests used in the treatment of breast cancer, organized by stage and clinical condition.*

Data Sources: *Systematic review of scientific literature, guideline recommendations, and data published by test manufacturers.*

Conclusion: *Several molecular tests that analyze expression of cancer-related genes have been validated in clinical trials and are recommended by clinical practice guidelines to inform diagnosis and treatment decisions for personalized interventions.*

Implications for Nursing Practice: *Molecular testing has become an important part of patient care for those with breast cancer. Oncology nurses must understand this methodology to prescribe tests, interpret the results, and provide guidance to patients.*

Key Words: *Breast gene expression, molecular diagnostics, molecular test, breast cancer subtypes*

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Molecular testing has become increasingly important in the prevention, diagnosis, and treatment of breast cancer. There are a number of genetic and genomic tests that are standard of care. These tests are conducted on different tissue specimens, require various testing methodologies, and provide varying levels of clinical utility for patients. Oncology nurses are often asked to educate patients about these molecular tests and what the test results mean. Advanced practice oncology nurses must often order testing, interpret results, and provide initial explanation and guidance to the patient. The purpose of this article is to provide all nurses with an overview of the relevant molecular tests for diagnosis and treatment of patients with breast cancer. This review is organized by the stage and clinical condition in which molecular tests are used. It begins with a description of the role of gene expression tests in diagnosis and treatment of early stage invasive breast cancer, and ends with molecular testing in metastatic disease.

Somatic Markers in Diagnosed Breast Cancer

Breast cancer is a clinicopathologically heterogeneous disease with a wide range of outcomes that are not fully predicted by histologic features. Molecular variances between histologically similar tumors contribute to differences in clinical behavior and response to therapy. In addition to traditional histologic evaluation, molecular characterization of tumor cells by measurement of cancer-related gene expression (cancer biomarkers) has become the basis of novel breast cancer treatments.[1,2] The three most clinically useful molecular markers are estrogen (ER) and progesterone (PR) receptors, collectively referred to as hormone receptors, and human epidermal growth factor receptor type 2 (HER2/neu), also known as proto-oncogene neu. These three markers have well-documented prognostic value as well as predictive value for specific treatments.[3,4]

Based on both histologic characterization and molecular profiles, pathologists divide breast cancer into four major molecular subtypes: luminal A and B (which tend to be hormone receptor-positive), HER2 type, and basal-like (the majority of which are triple negative: ER-, PR-, and HER2-negative).[5-7] Additionally, some authors suggest a fifth category of normal breast-like tumors, which are poorly characterized and of uncertain clinical significance.[2]

Distinct breast cancer subtypes have unique sociodemographic, anthropometric, and reproductive characteristics,[8] as well as different prognoses and differential responses to therapy.[9] The majority (73%) of all breast cancers are ER-positive, of which over 70% are also PR-positive.[10] *HER2* gene amplification is observed in approximately 15% of invasive breast cancers.[11] Testing for hormone receptor status (ER and PR) and for HER2 constitutes the standard of care in breast cancer. The joint guidelines of the American Society of Clinical Oncology (ASCO) and the College of American Pathologists and endorsed by the National Comprehensive Cancer Center (NCCN) Breast Cancer Panel, recommend that the status of these three markers be determined in all new invasive breast cancers and breast cancer recurrences.[12-14] ASCO's Quality Oncology Practice Initiative now recommends HER2 testing for all newly diagnosed women with invasive breast cancer within 31 days of the first office visit, using either protein expression assay by immunohistochemistry (IHC) or gene amplification by fluorescence in-situ hybridization.[15] In most HER2-positive tumors, HER2 protein overexpression is the result of gene amplification. Therefore, both tests provide equivalent information. The ASCO/College of American Pathologists guidelines do not specify preference for either test, but if results are equivocal, they recommend that reflex testing be performed using an alternative assay.[16] For ER and PR proteins, IHC is the method of choice,[12] although it should not be the sole basis for classification because low-staining ER-positive tumors have clinicopathologic features similar to those of ER-negative tumors.[17]

The majority of tests discussed in this article provide information about the molecular biology of the tumor. Tests to identify a patient's hereditary risk of cancer and the presence of germline mutations in *BRCA1* and *BRCA2* genes are discussed elsewhere in this issue. It is important to note that, although rare, it is possible for germline mutations in single genes to be discovered when patients undergo tumor genomic testing.[18] However, the primary purpose of tumor testing is to identify patients who could benefit from specific hormonal or antibody treatments directed against the receptors, in addition to, or instead of, standard cytotoxic chemotherapy and other pharmacological interventions. Cytotoxic drugs are directed against all rapidly dividing cells and thus kill mostly cancer cells as they progress through the cell cycle. However, normal cells are also affected, which result in a number of potential side effects. Targeted therapies directed against specific proteins made by cancer cells (ER, PR, HER2) can be less invasive and have fewer side effects than cytotoxic chemotherapy. The major benefit of biomarker-driven targeted therapy is the ability to customize treatment to the specific cancer subtype, provide treatment that is matched to the patient's tumor, and potentially avoid treatment that may not be as effective.

Additional Biomarkers

Specific recommendations for treatment and additional testing depend on the initial diagnosis status of the three major biomarkers (ER, PR, and HER2) in conjunction with other clinical findings (tumor grade, stage, lymph node involvement). Studies suggest that several other