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Review

Gene expression profiling in breast cancer: A clinical perspective

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ABSTRACT

Gene expression profiling tests are used in an attempt to determine the right treatment for the right person with early-stage breast cancer that may have spread to nearby lymph nodes but not to distant parts of the body. These new diagnostic approaches are designed to spare people who do not need additional treatment (adjuvant therapy) the side effects of unnecessary treatment, and allow people who may benefit from adjuvant therapy to receive it. In the present review we discuss in detail the major diagnostic tests available such as MammaPrint dx, Oncotype dx, PAM50, Mammostrat, IHC4, MapQuant DX, Theros-Breast Cancer Gene Expression Ratio Assay, and their potential clinical applications.

Introduction

A number of prognostic and predictive factors predict for future recurrence or death from breast cancer. The strongest prognostic factors are patient age, comorbidity, tumor size, tumor grade, number of involved axillary lymph nodes, and possibly biomarker status (e.g., HER2, estrogen, and progesterone receptors). Algorithms have been published estimating rates of recurrence and a validated computer based model (Adjuvant! Online for breast cancer)[1,2] is available to estimate 10-year disease-free survival that incorporates all of the above prognostic factors except for HER2 tumor status. Guidelines from professional societies, such as the St Gallen International Breast Cancer Expert Panel, The National Institute of Health (NIH) Consensus Criteria,[3] the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN), have recommended that the decision to use systemic adjuvant therapy requires considering balancing risk of disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of the therapy and comorbidity.[4,5]

Gene-expression profiling studies have led to an innovative molecular classification of breast cancer into four distinct subtypes[6]: the basal-like subtype, which is estrogen receptor (ER)-negative and HER2-negative; the HER2 subtype, characterized by increased expression of HER2 and of genes mapping to the HER2 amplicon; and two luminal ER-positive subtypes: luminal A, characterized by high levels of ER and ER-related genes, and luminal B, characterized by lower ER levels and high expression of genes implicated in the proliferation process. These newly defined molecular subgroups have distinct clinical outcomes.[7–9] Luminal A tumors are extremely sensitive to endocrine therapy and have a more favorable natural history than basal-like and HER2-like tumors notwithstanding the greater sensitivity of the latter tumors to chemotherapy.[10]

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The aim of gene-expression profiling technology is to provide a better prediction of clinical outcome than the traditional clinical and pathological parameters. This tool has been developed to further aid clinician in objectively estimating outcome with local treatment only, and also assist in estimating the absolute benefits expected from systemic adjuvant endocrine therapy and chemotherapy. However, the identification of low-risk patients not needing adjuvant chemotherapy, and tailoring therapy in relation to the RNA transcripts produced by cancer cells remains a challenge. In this paper, we review the gene expression signatures currently commercially available and discuss their limits and applicability to clinical practice in terms of personalized treatment.

Available tests, technical issues and feasibility

Tumor gene signatures were initially developed to help clinicians address the two main questions related to the management of breast cancer patients: "Should adjuvant treatment be prescribed?" and "Which type of adjuvant treatment should be prescribed?". Among the computerized tools devised to address these challenges, Adjuvant! Online is probably the most popular (www.adjuvantonline.org). Similarly, many molecular analyses that explore tumor gene signatures have been reported to be prognostic or predictive of the clinical outcome of breast cancer, and easy to incorporate in routine clinical practice.[11,12] However, before entering into routine use, it should be demonstrated that these novel gene predictors really add new independent information, and that they are reliable tools for decision-making at an individual level.[13] Finally, given the costs of these tests, we should evaluate in how many cases the gene predictors could change our practice, and whether they are cost-effective on a large scale.

Methods have been proposed to grade the evidence used in stratifying cancer risk to accommodate newer study designs that are emerging as a consequence of biomarker development. The efficacy of new tests is usually evaluated based on their clinical validity and clinical utility. Clinical validity defines the ability of the test to accurately and reliably identify or predict the intermediate or final outcomes of interest.[14] This is usually reported as clinical sensitivity and specificity. Clinical utility defines the balance of benefits and harms associated with the test, and should include improvement in measureable clinical outcomes and use.

In the present review, we describe the potential clinical uses of the currently available gene signature tests and their clinical validity as reported in the studies available (Table 1).

Methods

Identification of published reports

Studies were identified by a computerized search of the Medline (1966–2012), Cancerlit (1966–2012), and Embase (1990–2012) databases using the following text words: "gene arrays, breast cancer, gene expression profiling, MammaPrint, Oncotype DX, Mammostrat, Immunohistochemistry panel, Recurrence score, Theros, Genomic Grade Index, MapQuant, PAM50, Breast Bio-Classifier". We limited the search to English-language articles on human research that were published between 1966 and February 2012. A computerized search of the proceedings of the annual meetings of the American Society of Clinical Oncology (ASCO) held between 1998 and 2012 was also run to identify relevant studies published in abstract form. Lastly, all review articles and all cross-referenced studies from retrieved articles were screened for further pertinent articles.

Table 1
Gene predictor tests available in the clinic setting.

Test	Reference	Company	Tissue requirements	Technique	Output/Score
MammaPrint® (FDA approved)	van't Veer LJ et al., Nature 2002	Agendia BV, (Amsterdam, Netherlands)	Tissue core sampled on fresh specimens to be preserved in RNA later and immediately sent to the company; as an alternative, frozen archival material.	Microarray-based gene expression profiling	**2 Categories of** tumors with different **risk** to develop metastasis at 10 years - **low-risk** tumors (13%) - **high-risk** tumors (56%)
Oncotype DX™	Paik S et al., N Engl J Med 2004	Genomic Health Inc. (Redwood City, CA, USA)	Either fresh frozen or FFPE archival tissue	qRT-PCR (21 genes)	**Recurrence score** (0–100): predicts the risk of 10-year distant recurrence in ER-positive, lymph node negative patients - **low** (<18) - **intermediate** (18–31) - **high** (≥31)
Theros-Breast Cancer Gene Expression Ratio Assay®	Ma XJ et al., Cancer Cell 2004	Biotheranostics (Biomérieux Alliance Groupe, San Diego, USA)	Either fresh frozen or FFPE archival tissue	qRT-PCR (3 genes)	**HOXB13: IL17R ratio** stratifies ER-positive breast cancer into low or high risk for recurrence and is predictive of benefit from endocrine therapy
PAM50/Breast BioClassifier™	Parker JS et al., J Clin Oncol 2009	University Genomics, Inc./ARUP Laboratories	Either fresh frozen or FFPE archival tissue	qRT-PCR (55 genes)	**Continuous risk of recurrence**
MapQuant Dx™	Sotiriou C et al., J Natl Cancer Inst 2006 and Toussaint J et al., BMC Genom 2009	Ipsogen (Breast Cancer Profiler)	Either fresh frozen or FFPE archival tissue	qRT-PCR (8 genes)	**Genomic Grade Index** Divides histologically defined G2 tumors into: - GGI low-grade - GGI high-grade
Mammostrat®	Ring BZ et al., JCO 2006	Applied Genomics, Inc., (Huntsville, Alabama)	Either fresh frozen or FFPE archival tissue	IHC (5 proteins by 5 monoclonal abs)	**Mammostrat risk score**: high, moderate, or low risk of recurrence after tamoxifen treatment

Abs: antibodies; FFPE: formalin fixed paraffin embedded; GGI: Genomic Grade Index; IHC: immunohistochemistry; RT–PCR, reverse-transcriptase polymerase chain reaction.