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EDITORIAL

Gene-expression profiling in breast cancer: bespoke cancer therapy or more fiction than science?

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Breast cancer is the most common life threatening malignancy in women. Despite advances in molecular therapeutics, many patients with apparently early stage and curable disease still develop progressive and fatal systemic disease. Haffty et al. [1] demonstrated that despite conservative surgery and radiation followed by administration of chemotherapy in early-stage (T1 tumours) breast cancer patients, the distant metastasis-free survival rate was 71% at 5 years in patients with triple negative disease and 83% at 5 years in non-triple negative. These patients have potentially been under-staged by conventional staging, and therefore may not have received optimum therapy due to their misleading clinical disease profile. Conversely, patients receiving systemic therapy may not derive any additional benefit. Breast cancer is an intricate genetic milieu characterised by numerous molecular alterations that prevents standardising therapeutic strategies to all patients. Until recently, it has been difficult to accurately profile and predict the biological properties and clinical behaviour of breast tumours, however, with the development of DNA microarray technology, it is now possible to analyse the RNA expression of several thousands of genes simultaneously. The clinical application of this technology has the potential to signal a paradigm shift in patient selection for systemic therapy.

First, it provided a new molecular classification of breast cancer. This classification was proposed by Perou et al. [2], and subdivided breast cancers into four classes. Luminal-A cancers are ER-positive and mostly low grade. Luminal-B cancers are also ER-positive but tend to be high grade. Basal-like cancers are triple negative and Her-2-like cancers are Her-2 positive and usually ER negative. Currently, there are a number of validated commercially available multigene assays that identify expression of distinct sets of genes in breast cancer: Mammaprint (Agendia), Oncotype DX (Genomic Health), MapQuant and H/I (AvariaDX) (see Table 1 for comparison of assays). Mammaprint uses DNA microarray technology, whereas Oncotype DX and H/I use real time PCR based assays. These assays accurately predict the potential for disease recurrence and enhance patient selection for chemotherapeutic strategies.

Mammaprint uses a 70-gene predictor and is involved in the MINDACT (Microarray In Node negative Disease may Avoid ChemoTherapy) trial [3]. The objective is to administer chemotherapy to patients deemed at high risk of recurrence, and hormonal therapy only to low risk patients, as determined by the Mammaprint gene profile. Having recruited large numbers of patients who are stratified based on the clinical and pathological risks, it is hoped that this study will provide important information regarding the prognostic capabilities of the Mammaprint test and also validate its use in identifying women associated with improved survival. Previously, Buyse et al. [4] demonstrated that Mammaprint outperformed Adjuvant Online in predicting survival in an independent group of patients. Unfortunately, however, a major disadvantage of Mammaprint is that it requires fresh tissue for analysis, which may make its clinical integration difficult. The Oncotype DX and H/I assay, however, can use archival tissue (tissue from original biopsy) and may be more readily applied to the clinical setting. By analysing the expression of 21 known genes, Oncotype DX accurately determined the prognostic outcome in hormone receptor positive cancers post adjuvant tamoxifen in a retrospective cohort of 668

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Table 1 Comparison of commercially available genomic assays

Variable	Oncotype DX	Mammaprint	Theros	MapQuant Dx
Type of assay	21-gene	70-gene	2-gene ratio	97-gene
Tissue	Formalin-fixed, paraffin embedded	Fresh/frozen	Formalin-fixed, paraffin embedded	Fresh/frozen
Cost	US $3,500	US $3,500	n/a	n/a
Technique	Q-RT-PCR	DNA microarrays	Q-RT-PCR	DNA microarrays

Q-RT-PCR quantitative reverse-transcriptase-polymerase chain reaction

patients [5]. This was also validated by Habel et al. [6], who demonstrated that Oncotype DX was an accurate predictive test for ER-positive, node negative breast cancer patients who did not receive chemotherapy but offered tamoxifen. Furthermore, TAI-LORx (trial assigning individualised options for treatment) aims to assess the role of Oncotype DX as an accurate predictor of chemotherapeutic response for ER-positive and node negative tumours [7].

Numerous studies have examined gene profiles that are associated with tumour response to certain chemotherapeutic agents in both the adjuvant setting (adriamycin/cyclophosphamide, docetaxel) and the neoadjuvant setting (paclitaxel/fluorouracil/cyclophosphamide/doxorubicin) [8–11]. In addition, recent studies have also suggested that deletion and amplification of the topoisomerase II alpha (TOP2A) gene is a poor prognostic indicator and is predictive of an enhanced response for HER2 positive tumours to anthracycline-containing than to non-anthracycline-containing regimens10. Also the CYP2D6 enzyme is crucial in the metabolism of tamoxifen to its active metabolite and potent antiestrogen endoxifen. A subset of patients with low or completely deficient levels of CYP2D6 cannot activate tamoxifen, and are therefore unable to benefit from its antitumor effects [12, 13]. A commercially available assay has now been developed which can identify these CYP2D6 deficient patients, AmpliChip (Roche Diagnostics Inc., Indianapolis, IN, USA). It is hoped that these tamoxifen insensitive CYP2D6 deficient patients with newly diagnosed breast cancer, may now receive an alternative adjuvant hormonal therapeutic strategy rather than tamoxifen. Combined, these studies demonstrate the potential to identify genes which will determine the level of response to a given treatment regimen. However, it is difficult to predict how soon these evolving technologies will be integrated into clinical practice. However, this promising technology has been evolving over the last 5 years and yet despite endorsements from the Food and Drug Adminstration (FDA), the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN), there is a surprising lack of robust prospective data. Currently, there are only two prospective randomised trials comparing genomic testing and clinical factors. The results of the European MINDACT Trial and the American TAI-LORx Trial are eagerly awaited to determine the future application of gene-expression technology in the clinical setting [3, 7]. Interestingly, a prospective multi-centre study, which examined the effectiveness of Mammaprint when used in conjunction with clinical guidelines, demonstrated an alteration in adjuvant treatment in 26% of patients [14]. In addition, a retrospective analysis of the impact of OncotypeDX low recurrence score results on treatment decisions demonstrated a change in management strategy in 30% of patients [15]. These findings suggest that this expensive technology may alter patient care in approximately one-third of cases and the clinical impact in terms of survival benefit of this alteration has yet to be determined. Genetic profiling of patients and their tumours promises to accurately select patients with a high/low risk of recurrence and more importantly predict their response to certain chemotherapeutic agents. However, until additional randomized studies with large cohorts of patients with various tumour types and stages are completed, it remains as only a promise. The integration of this technology into the clinical setting is dependent on the completion of ongoing trials and until this data is available and appropriately validated, gene-expression profiling is best used as an adjunct to current clinical algorithms. This technology has and will continue to enhance our understanding of oncogenesis, however, it is currently unclear how these advances will ultimately impact on future breast cancer therapy and patient care.

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