



# Utility of gene expression signature in treatment decision of breast cancer

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Breast cancer is the most common cancer and a leading cause of cancer-related mortality in women worldwide. About 1.7 million women were diagnosed with breast cancer in 2012 and 6.3 million women were alive with breast cancer in the previous five years (1,2). Despite modern therapeutic interventions, the 5-year survival rate of breast cancer has improved only marginally and its recurrence is observed in more than 50% of the patients (3,4). Treatment failure and recurrence of breast cancer can be attributed to multiple factors which are difficult to predict for a particular patient (5). Genomic tests such as Oncotype DX, MammaPrint, miRNAs and other molecular and clinico-pathological markers are often employed for guiding therapeutic decisions (6-13) but it is difficult to say which test is reliable. Subtyping of breast cancer is largely based on estrogen/progesterone receptor (ER/PR), and human epidermal growth factor receptor 2 (HER2)/neu status and the most aggressive form is considered to be triple negative breast cancer (TNBC) (14), the drug resistance and recurrence rate of which is extremely high (15-17). Most alarmingly, TNBC has recently been found to be prevalent in as high as 74% of premenopausal women below 35 year of age (18). However, there exists no TNBC-specific therapeutic target yet.

Women with early-stage breast cancer are often treated with systemic therapy including chemotherapy, radiotherapy, endocrine therapy and drugs against HER2, or various combination of all these. Treatment decisions are based primarily on the clinicopathological characteristics such as hormone receptor status, HER2 status, tumor

grade, size, lymph-node, age and menopausal status.

Recently, in an ingenious large phase III study “70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast cancer” (*NEJM*, Vol. 375:717-29, August 25, 2016; doi: 10:1056/NEJMoa1602253) by Cardoso and colleagues demonstrated a novel clinical utility of MammaPrint, a 70-gene expression signature in correlation with clinico-pathological characteristics in deciding whom to give or not to give highly toxic chemotherapy among early stage breast cancer patients (19). This 5-year follow-up study was carried out from 2007 to 2011 by enrolling 6,693 early stage breast cancer patients at 112 institutions from 9 European countries and the subjects were randomized for surgery and adjuvant chemotherapy or no chemotherapy. The patients were categorized in 4 groups on the basis of the 70-gene expression signature as ‘genomic risk’ along with ‘clinical risk’ indicated by specific clinicopathological features in deciding systemic adjuvant chemotherapy taking the treatment outcome or end point of the study as 5-year disease free survival without distant metastasis. The 4 groups classified were (I) high clinical risk & low genomic risk; (II) low clinical risk & high genomic risk; (III) high clinical risk & high genomic risk; and (IV) low clinical risk & low genomic risk. The study concluded that women with early stage breast cancer who are at high clinical risk and low genomic risk for relapse of the disease have 1.5 times lower rate of distant metastasis free 5-year survival than those are given chemotherapy. In other words, if this group of early stage breast cancer patients are given chemotherapy they will have 1.5 times more survival rate than those not

provided with chemotherapy. Authors have proposed an innovative hypothesis wherein a patient can avoid severe adverse effects of chemotherapy as it may not be necessary for this specific subtype of early stage breast cancer patients. Though this appears to be an excellent proposition, the very results/outcome of the study which has not been compared with studies of other groups (13), raises pertinent ethical questions including several scientific questions on study protocol that the investigators have followed in defining the clinically high and genetically low risk groups.

Any stringent strategy of treatment which may have any amount of severe adverse health effects, it is well acceptable and worthwhile even if it can save one woman's life. In this study, early stage breast cancer patients have 1.5 times more survival rate when chemotherapy is given than those are not given chemotherapy. The 1.5 times higher survival is no less important rather statistically highly significant when the number of patients is large. Therefore, the early stage breast cancer patients cannot be denied the desired chemotherapy to allow them for cancer recurrence and metastasis. However, it would have been highly interesting if a subtypes within this 'high clinical and low genomic' risk group could be further stratified with specific either clinical or genomic risk determinants or any additional novel genomic/epigenomic, or transcriptomic (including specific miRNA signature) or proteomic biomarkers to differentiate between those required chemotherapy and those do not.

For classification, along with genomic data, mainly tumor grade, hormone receptor status, HER2 status, nodal status and tumor size have been taken into account. However, there have been huge deviations from the standard assessment of clinical risk factors. It is clear from supplementary table 13, that a prime importance is given to tumor size in making the clinical risk assessment and chemotherapy decision. Even if the patients are ER/PR-ve, HER2-ve and either well, moderate or poorly differentiated, with or without axillary node and of any tumor size, they are arbitrarily categorised as low or high clinical risk and all were given chemotherapy only if their genetic risk is high. It indicates that chemotherapy decision is completely dependent on genomic risk only though it is yet to be established that 70 gene expression signature is solely the gold standard for progression and reoccurrence of early stage breast cancer. It suggests that genomic risk, though not elaborated, is of prime importance and critical for molecular stratification of early stage breast cancer and deciding their treatment strategy. It has been demonstrated that at 5 years, the rate of survival without distant metastasis

would have been 95.0% with the clinical-risk alone and 94.7% with the genomic-risk alone. But the rate of survival without distant metastasis in high clinical and low genomic group was 94.7% [95% confidence interval (CI), 92.5 to 96.2] among those not receiving chemotherapy. In fact, breast cancer survival rate is generally very high, often more than 5 years; for example, recurrence of ER positive tumours occurs very late, so 5-year is very less time to judge the utility of this hypothesis to predict the survival without distant metastasis. Also in supplementary figures S2, S3, S5 and S6, the 5-year distant metastasis free survival was not statistically significant. Therefore it would be interesting to examine this hypothesis for at least 10-year survival and these results will be of immense importance in deciding if early stage breast cancer patients need to go for chemotherapy or not. Several authors also demonstrated that, the luminal A subtype of tumors are associated with late recurrence in the univariate ( $P=0.0001$ ) analysis. In multivariate analysis, the non-luminal a phenotype of tumors significantly increased the risk of early tumor relapse (OR: 3.26; 95% CI, 1.01–10.59) (20-22). Positive ER status is associated with a good response to hormonal therapy, and a long disease-free and overall survival after chemotherapy (23). Ross *et al.* [1999] demonstrated that HER2 protein overexpression is associated with aggressive tumor phenotype with early tumor relapse, node positivity and high tumor grade. These patients are invariably given chemotherapy even if they are in early stage breast cancer (24). In case of hormone subtypes, the non-luminal, HER2-positive: ER-negative, PR negative and triple negatives are at high clinical risk but even if they are of low genomic risk, these patients are often recommended for chemotherapy as their recurrence rate is very high and early.

HER2-positive breast cancers are aggressive and fast-growing, and commonly used drug trastuzumab (Herceptin) has been shown to dramatically reduce the risk of relapse in early-stage breast cancer. However, these cancers have been categorised as clinically high and genomically of low risk category and are not to be given chemotherapy. However, several large, multicenter adjuvant therapy trials demonstrated that the addition of trastuzumab to systemic chemotherapy reduces recurrence by approximately 50% and improves overall survival by 30% (25-27). Additionally, in ductal carcinoma in situ (DCIS), the early stage node positive tumors, radiotherapy is generally given to prevent recurrence (28). But in this study, no patient has been considered for radiotherapy.

Therefore it is not advisable to have a generalized treatment decision not to use chemotherapy for all early stage breast cancer patients such as triple negative, node positive tumors with micro metastasis. Without chemo or radiotherapy, patients have every chance to relapse specifically after breast conservation surgery. If a single cancer or cancer stem cell survives after surgery, it is likely to cause early relapse, distant metastasis and aggressive cancer.

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