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Genomic Biomarkers for Personalized Medicine in Breast Cancer

Review Article

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Introduction

DBreast cancer is the most common malignant disease in Western women. Historically, breast cancer was perceived as a single disease with various clinicalpathological features, and therefore, "one drug fits all" approaches drove the treatment regimens. The advent of genomics studies has led to a new paradigm in which breast cancer is heterogeneous consisting of different diseases from the same organ site. For example, gene expression profiling analysis revealed that estrogen receptor (ER)-positive and ERnegative breast cancer are two distinct diseases with different risk factors, clinical presentations, outcomes, and responses to systemic therapies [1]. Consequently, the new paradigm demands a personalized strategy in cancer medicine, in which the selection of treatment regimens for each cancer patient will largely rely on assessment by predictive biomarkers and study of the anatomical and pathological features of the cancer.

Adjuvant chemotherapy is still the major therapeutic option used to reduce recurrence after surgery for advanced breast cancer cases as well as some early-stage breast cancer cases. In this area, the assessment of anatomical and pathological features of cancer is the mainstream practice to determine whether a patient needs to undergo chemotherapy. However, this strategy did not correctly predict prognosis for a large number of patients [2]. For example, a global survey estimated that out of ~ 60% early-stage breast cancer patients treated with adjuvant chemotherapy, only less than 15% ultimately derived benefit [3]. In other words, over 85% of these patients suffered from toxic side-effects associated with chemotherapy with limited benefit. Therefore, the clinicalpathological-guided approach is not sufficient for implementation of a personalized therapy; many overtreatment cases can be avoided if appropriate predictive biomarkers are available [4].

The personalized treatment of breast cancer has made great progress with predictive biomarkers [5]. Some biomarkers have been established, including the use of ER expressions to determine the benefit of tamoxifen therapy, human epidermal growth factor receptor 2 (HER2) expressions for trastuzumab treatment, and mutation of breast cancer susceptibility protein (BRCA) for inhibitors of poly-ADP(ribose) polymerase (PARP). For example, the adjuvant tamoxifen therapy has been well established to significantly reduce long-term risks of breast cancer recurrence in ER-positive patients [6]. Meanwhile, the overexpressions of HER2 gene products occur in approximately 20 to 25% of human breast cancers, and are associated with an aggressive behavior in tumors [7]. The subsequent development of trastuzumab has significantly reduced the rate of recurrence by approximately 50 percent, representing the largest benefit in early breast cancer to be reported since the introduction of tamoxifen in ER-positive disease [8]. More recently, the utility of PARP inhibitors was found from promising results in selected BRCA-mutated tumor cases including breast cancer [9], which might relate to the facts that the cancer cells in patients with BRCA mutations have an increased reliance on PARP to repair their DNA [10]. Although much safer than chemotherapy, the targeted therapies with companion biomarkers still held some severe toxicity concerns, such as the increased cardiac safety concern in the trastuzumab treatment [11], and overtreatment should be avoided.

The development of therapies to effectively treat the breast cancer patients with overexpression of HER2 has greatly inspired cancer genomic studies [12]. An enormous number of genomic biomarkers have been proposed for assessing tumor prognosis and predicting the sensitivity of chemotherapy [13]. The "70-gene signature" (MammaPrint™, Agendia) and "21-gene recurrent score" (Oncotype DX™, Genomic Health) were most widely accepted. The MammaPrint assay measures the expression of 70 genes from fresh or frozen breast cancer tissues using DNA microarray data to calculate a prognostic score to stratify patients into "good" or "poor" prognosis groups. The patients with "good" prognosis are likely to have no recurrence in 5 years and thus should not take adjuvant chemotherapy. In 2007, the U.S. Food and Drug Administration (FDA) has cleared MammaPrint as a prognostic tool for the lymph node negative breast cancer patients of under 61 years of age, ER negative or positive, with tumors of 5 cm or less. Additionally, retrospective studies revealed its sensitivity to predict responses to neoadjuvant chemotherapy in patients [14]. Currently, MammaPrint is supported by the level II evidence according to Tumor Marker Utility Grading System (TMUGS) devised by the American Society of Clinical Oncology (ASCO) panelists, suggesting its acceptance over the clinicalpathological features.

Oncotype DX measures the expressions of 21 genes from formalin-fixed paraffin-embedded tissues using multiple quantitative reverse-transcriptase polymerase chain reactions (qRT-PCR) to derive Recurrence Score (RS). RS, ranging between 0 and 100, assess a likelihood of breast cancer recurrence in 10 years. Patients with low-risk (RS lower than 18), intermediate-risk (RS between 18 and 31), and high-risk (RS greater than 31) correspond to the 10-year relapse rate of 7%, 14%, and 30%, respectively. This assay has been extensively tested in samples from randomized clinical trials, by which it is demonstrated as an independent prognostic factor and a predictive biomarker to assess the likely benefit from certain types of chemotherapy for patients with ER-positive, node-negative breast cancer treated with adjuvant tamoxifen. Supported by the level I, the strongest level of evidence of TMUGS, the Oncotype DX assay has been widely used in clinical practices in the USA. It has been included in the major guidelines issued by the National Comprehensive Cancer Network and ASCO guidelines to be used as tumor markers in breast cancer for decision making, and is also recommended by the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer.

The clinical application of MammaPrint and Oncotype assays helps to distinguish good-prognosis from poor-prognosis cancers, which may limit the thousands of cases of breast cancer patients suffering from toxic side-effects of chemotherapy while receiving little benefit [2]. However, there are still numerous claims in literature acclaiming the improved prognostic factors that have found limited utility for clinical application. The gap may be related to an unclear intended use of the genomic biomarkers or the inappropriate experimental design during the development [15, 16]. For example, Perou et al. [17] utilized a clustering analysis to discover that breast cancer is composed of at least four molecular subtypes based on gene expression patterns, including luminal (i.e., luminal A and B), HER2-enriched, basal-like, and normal breast like. These breast cancer subtypes have now become part of the standard terminology of breast cancer [1]. However, the clinical utility of the subtype classification as a molecular assay has been hindered for a long time by the fact that the genes and methodology used to define these subtypes is unclear. Until recently, a 50-gene signature was proposed for the standardization of breast cancer subtyping [18].

Despite the advances in genomic biomarkers, there is still a concern of overstating their utility for breast cancer management compared to their utility in other fields [19].

- Firstly, no sufficient published evidences demonstrates that these genomic biomarkers perform better than tumor morphology and basic immunohistochemistry for classifying patients by recurrence outcomes, or for predicting chemotherapy benefit [20]. A recent study indicated that an IHC4 (ER, PR, HER2, and Ki67) score measured from four standard immunohistochemistry markers can provide similar prognostic accuracy as Oncotype DX [21].
- Secondly, a meta-analysis of large cohorts of breast cancers revealed that the gene signatures are predominately composed of the proliferation-related genes, and these proliferation-related components contribute most to predict prognosis [22]. However, the heavily weighted proliferation-related gene signatures only work for ER-positive cancer but not for ER-negative. In the ER-negative cancer the proliferation-related genes usually have high expression.
- Thirdly, these signatures can predict benefits for general multidrug chemotherapy regimens, but met challenges to optimize "personalized" treatment predicting the response of specific chemotherapy agents [23].
- Fourthly, the patients with intermediate risk are still a huge challenge in decision-making using these genomic biomarkers. Several efforts have been initiated to assess the utility of genomic biomarkers for this category of patients. For example, a clinical trial called TAILORx was implemented to test patients with intermediate recurrence scores determined by Oncotype DX. Another clinical trial called MINDACT was also initiated to evaluate the patients with discordance assessed risk between AdjuvantOnline (a clinical tool for decision-making in adjuvant chemotherapy) and MammaPrint.
- Lastly, both Oncotype DX and MammaPrint cost over $4,000 for one test. Although they can be beneficial to patients by identifying good-prognosis from poor-prognosis cancers, the high cost still acts as a huge financial barrier for many patients.

Though the initial claim that genomic biomarkers will replace the clinicalhistological approach seems to be over optimal, gene expression profiling analysis has undoubtedly made a significant impact on our understanding of the biology of breast cancer and helped thousands of patients to spare unnecessary chemotherapy with improved life quality. The current genomic biomarkers provide limited benefit mainly due to their heavy reliance on proliferation-related genes. However, they can be further improved through a better understanding of the disease. For example, the genes related to other cancer mechanisms like invasive, metastasis, and immune response may be a better and more specific biomarker, particularly for the ER-negative breast cancer. Furthermore, microarrays that only measure the expression of the pre-defined genes are the current mainstream technology used for the discovery of genomic biomarkers, whereas the newly emerging next-generation sequencing technology provides a more sensitive and precise measurement of the whole-transcriptome sequence [24], which will inevitably lead to the identification of more predictive biomarkers and therapeutic targets. Notably, the Nature journal recently published a range of studies to present whole genome analysis of breast cancer and to provide a landscape of the genetic diversity in breast cancer, which vindicates refined tumor-classification strategies and potential new therapeutic targets [12, 25]. Besides the advances in technologies, the U.S. FDA and the National Institute of Health have embraced personalized medicine through adjusting the scientific and regulatory structure [5]. Very recently, a draft of FDA guidance for industry entitled "in vitro companion diagnostic devices" was published for comment, which emphasizes making personalized therapies feasible by identifying patients who can benefit (http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm262292.htm). Therefore, it is expectant that genomics biomarkers will continue to help moving the treatment of breast cancer toward personalized medicine.

Conflicts of Interest Statement

The views presented in this article do not necessarily reflect those of the US Food and Drug Administration.

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