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Molecular tools: advanced diagnostics for breast cancer.

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Introduction

Breast cancer is the most common and lethal carcinoma, commonly diagnosed in women. It is the second most cause of death followed by Lung cancer [1] with more than 1.7 million cases in the year 2012 (most recent available statistics) [2]. More than half of the cases were observed in the developed and industrialized nations [3,4]. This is doubtlessly credited to the accessibility of screening projects used to diagnose breast cancer, which may somehow would have never been diagnosed [5]. The overall costs for the treatment of breast cancer in patient persisting breast cancer increases with its higher stages. In this manner, screening breast cancer at an early stage both advantages the patient and minimizes the financial burden [6]. Molecular Diagnostics plays a crucial role in detection and management of Breast cancer. It not only helps provide personalized diagnostic information to the patient but also allows specific treatment plans which indeed help limiting resistance and reducing toxicity. This review briefly summarizes recent molecular techniques used for diagnostics of Breast cancer and provides updates with recent novel approaches in the field.

Routine Diagnostics

Hormone receptor testing

Receptors for Estrogen and Progesterone, Analyzing the presence of Estrogen Receptor (ER) and Progesterone Receptor (PR) are currently a routine evaluation of breast cancer samples. This test result indicates if any excessiveness of Estrogen and/or Progesterone, by determining the tumor cell expression of the receptors for ER and PR. ER expression is considered to be one of the most important biomarkers in breast cancer. The positive results are indicated as ER+/PR+ (if you have one or both receptors positive). Diagnosis for this test is determined by Immunohistochemical (IHC) assays showing positive results if intensity is >2 [7,8].

ER+/PR+ tumors can be treated with hormone therapy, by blocking the Breast tumor cells from getting the estrogen and progesterone which are required for the tumor cells to grow [9].

HER2/neu analysis

Human Epidermal growth factor Receptor 2 (HER2) is the second most prognostic marker currently recommended for the evaluation for the primary invasive breast cancer. HER2 is a protein found on some breast cancer cells. HER2 gene overexpression is found to be in 25% of breast cancers [10]. Scholarly studies reports, overexpression of HER2 gene leads to twice the mortality rate in comparison to the women with HER2 negative expression [11].

HER2 is currently evaluated using IHC and Fluorescence in situ Hybridization (FISH), for protein expression and gene expression, respectively. FISH is also a confirmatory test for IHC unclear positive (+2 score) HER2 status. Recently, Monogram Biosciences released, HERmark™ breast cancer assay to improve the current methods for HER2/neu analysis [12]. Breast cancer patients with HER2 positive status are treated with target medication therapy specifically targeted to the receptor.

Prediction using Molecular Signature

Recent progress in the realm of genomics helps identify gene expression patterns that have prognostic and predictive value in breast cancer [13]. These techniques are based on messenger RNA level analysis by reverse transcription Polymerase Chain Reaction (RT PCR) or microarray-based assay. The results are then converted into mathematical algorithms to predict scores using quantitative analysis. There are few of the several commercially available common gene expression tests are, Mammaprint™ (Agendia), OncotypeDX® (Genomic Health), Theros H/I SM and MGI SM (Bio therapeutics).

Mammaprint ™

Mammaprint™ was cleared by FDA in 2007 and involves a combine measurement of multiple genes and other analytes for an in vitro diagnosis to determine predictive and prognostic values and information. It is often referred to as "gene expression profiling" in the literature as it is largely based on mRNA level and measures for selected genes. Mammaprint ™ measures 70 genes expression found in the tumor cells using microarray platform and reports results as either low risk or high risk prediction for recurrence of the disease [14]. The results along with the prediction help in characterizing the cancer for treatment. It is now being validated in both lymph node positive and lymph node negative breast cancer [15,16]. The test is used for stage I and II breast cancer with <5 cm length in patients who are younger than 55 years of age [14].

OncotypeDX®

As like Mammaprint™, Oncotype DX® is a Multianalyte Assays with Algorithmic Analysis (MAAA) but with no FDA requirement in contrast. It is used in accessing the prognostic information using qRT-PCR analysis of 21 genes found in the tumor cells. It is validated for ER+, HER2-, node-negative and node-positive cancer [17,18]. The test results are reported using a formula to calculate the recurrence score further characterizing into Low, Medium and High (0-100 score) [19]. This score is also used for the treatment purpose for that patient. The test is used for stage I and II breast cancer but can also be used for Ductal Carcinoma in situ (DCIS) [20].

Theros H/I SM and MGI SM

Theros H/I SM is a molecular diagnostic test, measuring the ration of gene expression of genes HOXBI3:IL17BR. It helps predicts the clinical outcome for breast cancer patients treated with tamoxifen [21]. Resistance to tamoxifen is been associated with an increased level of gene expression resulting into aggressiveness of the tumor [22].

Theros MGI SM is an additional test that profiles for 5 gene expressions helping understand the recurrence pattern of the ER+ breast cancer and reclassify Stage II tumor into Stage I like or Stage III like outcomes [23]. mRNA samples from formalin fixed paraffin embedded (FFPE) tissues is extracted and q RT-PCR is used to quantify the gene expression. If both tests are used together, demonstrates potential advantages over current diagnostic techniques [24].

Next Generation Sequencing of Breast Cancer Tissues

To identify an active mutation in the tumor, Next Generation Sequencing (NGS) has made it possible to sequence hundreds of genes in the tumor cells [25]. It helps sequence multiple genes by "gene panel testing" and is offered by many laboratories. Prime advantage of NGS over single gene testing, includes the potential to sequence large number of genes in one single panel. It helps detects all possible genetic variations and mutations [26]. It is cost effective and requires less time with compare to single gene testing. Since, NGS provide systemic results with all tissue samples irrespective of ER/PR status; it helps in personalized therapy for treating breast cancer [24].

Conflict of Interest

The author declares no conflict of interest.

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