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Role Of Molecular Testing In Breast Cancer Management Plans

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IMPORTANCE The role of genomic testing in hormone positive breast cancer has been recently debated in scientific literature and the guidelines for breast cancer are improving with addition of genomic testing in terms of categorization of the tumors according to their malignant potential and their response to chemotherapy. The objective of this review is to highlight the role of molecular testing specifically in breast cancer. The most commonly used gene panel is Oncotype Dx, which has been compared with other available gene panels. The incorporation of molecular testing in international guidelines will likely save patients from unnecessary chemotherapies and under or overtreatment in several scenarios.

KEYWORDS Oncotype Dx, Molecular Testing, Breast Cancer

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Commentary

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The management plans are shifting from prognostic indexing to a more personalized approach in form of molecular testing to judge the malignant potential of malignancies and then devising personalized treatment plans. Multiple prognostic systems have been previously developed which include Manchester score for small cell lung cancer, MACIS score for papillary carcinoma thyroid, and Nottingham scoring system for carcinoma breast. The dilemma of the conventional scoring system was that they were all dependent on factors like age, tumor size, and grade of tumor, however, none individualized personal risk and reflected a person's response to disease in terms of his or her genetic makeup. The paradigm of prediction and recurrence scoring system has now been shifted towards molecular testing that is individual-based and provides us with genetic assay which makes us wise regarding an individual's response to a disease progression and patient's survival regardless of the treatment regime given.

The Oncotype dx is a genomic testing tool that predicts the beneficial effects of chemotherapy along with hormonal therapy, it involves 21 genes and two types of tests one is for early ER-positive, HER 2neu negative carcinoma breast while another one for already diagnosed DCIS. The risk stratification involves (0-25) as low and (>31) as high. The presence of Oncotype Dx has produced a remarkable change in utilization of chemotherapy for early-stage ER-positive HER2neu negative, node-negative carcinoma breast, ensuring prescription of systemic treatment to high-risk patients while low-risk ones are treated with hormonal therapy solely.

The role of Oncotype dx has been studied in terms of its effects on hormonal therapy, adjuvant therapy, and recently neoadjuvant therapy as well. The NSABP-20 study proves that Recurrence Score (RS) can be used for prediction of patients with node negative, ER positive carcinoma in whom adjuvant chemotherapy will be beneficial for survival and disease-free period compared to hormonal therapy alone[1]. A study published in EJSO, has studies impact of Oncotype Dx RS scores on adjuvant chemotherapy using a group of 201 patients recently diagnosed as ER +, PR – Her 2-neu negative. In all of them chemotherapy was advised by a multidisciplinary team, but Oncotype Dx scoring reduced the figure to 127/201 allowing only 63.2% to get chemotherapy. In node-positive patients, 69.2% were spared of chemotherapy[2]. TAILORx trial concluded that in patients with high RS score, utilization of adjuvant chemotherapy significantly reduces recurrence of cancer and mortality, while patients with low RS score do not gain any additional benefits from chemotherapeutic agents[3].

To fully understand the role of Oncotype Dx in the setting of neoadjuvant chemotherapy we should be fully aware of terms e.g. pathological complete response (pCR), Partial remission, and Disease progression. pCR refers to the complete clinical absence of tumor after neoadjuvant chemo or radiotherapy while Partial remission refers to a mere decrease in the size of the tumor and disease progression means an increase in disease burden after the first line of therapy. Previously neoadjuvant chemotherapy has aided us in opting for breast conservation surgery and sparing patients of unnecessary axillary clearance. Multiple studies have been done on the effects of Oncotype Dx regarding neoadjuvant chemotherapy. One study concludes that opting NAC (neoadjuvant chemotherapy) upon results from Oncotype Dx permits the application of treatment correctly and prevents chemotherapy in approximately half of the patients previously selected for

NAC based on clinical parameters. In this study the researchers have found that 35% of the patients had a high RS (>25) that would advocate long-term chemotherapy[4]. National cancer database executed a large-scale study to analyze the role of Oncotype Dx for predicting the response of neoadjuvant chemotherapy. The researchers found that ER-positive, HER2-neu negative patients with high RS were more likely to have a complete pathological response[5].

Role of Oncotype dx was also studied for prediction of axillary response to neoadjuvant chemotherapy[6]. This study included patients with T1-T2 and N1-N2, ER-positive, HER2-neu negative disease. RS was established as low (<18), intermediate (18-30), high (>30). A total of 158 patients were studied out of which 35.4% were categorized as low RS, 39.2% as intermediate RS, 25.3% as high RS, pathological complete response was observed in totally in 14.6% of patients, out of which 47.8% belonged to high RS score category, 26.1% had an intermediate score and 26.1% had low RS score hence proving that most patients who achieved pathological complete response belonged to high recurrence score category[6].

Multiple other molecular tests used for hormone positive carcinoma of the breast include Mammaprint, Endopredict, Prosigna risk of recurrence, Breast Cancer Index, and Oncotype Dx. Oncotype Dx is the only score that is endorsed in most international guidelines, tells us about the prognosis of disease, its recurrence, and predicts beneficial effects of adjuvant chemotherapy along with hormonal therapy.

Comparison of Oncotype Dx with other molecular tests

There is a growing consensus now about the role of molecular testing of hormone positive cancer for prescribing neoadjuvant chemotherapy. Increased incorporation of Oncotype dx is being observed in trials as well as in clinical implementations of treatments. NICE endorses usage of Oncotype Dx in decision-making for chemotherapy[8]. Moreover, Oncotype DX has been incorporated in other international guidelines like (NCCN)[9], European Society of Medical Oncology (ESMO)[10].

In the coming years, we can expect Oncotype Dx and molecular testing as a promising tool in decision making which is accurate and cost-effective and has advantage of sparing unnecessary chemotherapies and surgeries.

Table 1. Comparative analysis of molecular analysis systems in breast cancer management. (Adapted from Gruz O et al. Breast Care 2013)

	Oncotype Dx / Recurrence Score	**PAM50/ Prosigna Risk of Recurrent**	**Mammaprint**	**EndoPredict**	**IHC_4**	**Breast Cancer Index**
Classification	Continuous score 0-100(RS): L/IM/H risk (<18/18-30/231)	Continuous score 0-100 (RoR ± turn our size): L/M/H risk (<40/41-60/>60 in NO and <15/16-40/>40 in N1)	Two groups: L/H risk	Continuous score reported asL/H risk	Three groups L/M/H risk	Continuous score is 0-10: L/M/H risk
Prognosis	YES	YES	YES	YES	YES	YES
Prediction of endocrine therapy benefit	YES	NO	NO	NO	NO	YES
Prediction of chemotherapy benefit	YES	NO	NO	NO	NO	NO
Guidelines recommendation	St Gallen [2], NCCN [3], NICE [4], ASCO [5], ESMO [8]	St Gallen [2](prognostic)	St Gallen [2](prognostic)	St Gallen [2] (prognostic)	NO	NO
Level of evidence	Prognosis: IB Prediction: IB	Prognosis: IIB	Prognosis: BC	Prognosis: IB	Prognosis: IIB	

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