



Letter to the Editor

To Give or Not to Give Adjuvant Chemotherapy in Breast Cancer? Can CanAssist Breast Assist?

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Survival of early-stage hormone receptor (HR)-positive and human epidermal receptor 2 (HER2)-negative breast cancer has significantly improved over the last three decades. Adjuvant chemotherapy plays an important role in this advancement.¹ However, we have also learnt that the benefit of chemotherapy is not for all patients.² Some patients may be overtreated with chemotherapy resulting in avoidable toxicity. Some may be undertreated resulting in lack of cure. Therefore, a predictive biomarker is of great demand. Such a biomarker will help the oncologist in deciding treatment course, whether to give or not to give adjuvant chemotherapy.

Over several decades of clinical trials, the field of breast oncology has finessed the art and science of medicine by individualizing therapeutic decision-making based on various clinicopathologic tumor-level factors like tumor size, nodal status, grade, HR and HER2 status along with patient factors like age, menopausal status, and comorbidities. But these parameters have limitations. For instance, an N1 disease may have an indolent biology and poor chemosensitivity. A small N0 disease may have an aggressive biology and be highly chemosensitive.

A paradigm shift in this field happened when RNA-based gene microarray assays involving 21 genes were shown to be both prognostic for outcomes and predictive for chemotherapy.^{3,4} Suddenly, oncologists woke up to the possibility that the decision-making can be well-defined based on the degree of expression of a panel of genes in a patient's tumor tissue.

There are now several types of products in the market—Oncotype DX (21-gene assay), MammaPrint (70-gene assay), Prosigna (50-gene assay), Endopredict (12-gene assay).

Oncotype Dx and MammaPrint are the more commonly used tests globally. Both these assays are validated in large prospective, multicentric, independent, phase 3 randomized controlled trials involving thousands of patients with more than 8 years of follow-up (TAILORX, RxPonder, MINDACT trials).

However, for patients living in low-and-middle-income countries (LMIC), the alley is still dark. Very few patients have access to these genomic assays due to the exorbitant cost. As a matter of fact, it is far more cost-effective for patients to complete the full schedule of dose-dense chemotherapy than opt for biomarker-driven decision-making. Another concern with these tests is the relatively low representation of non-Caucasian patients in the development and validation studies for these tests. In fact, a retrospective, population-based cohort study showed that Oncotype DX had lower prognostic accuracy in Black patients with early-stage breast cancer.⁵ None of the genomic assays currently recommended in international guidelines are validated for use in Indians. Therefore, the prognostic and predictive accuracy of these tests in Indians give some cause for concern.

In this context, Parikh et al. have proposed practical consensus recommendations to optimize treatment decision for chemotherapy use in patients with HR-positive and HER2-negative early-stage breast cancer in India.⁶ The consensus was achieved with the help of review of published evidence, practical experience, discussion among the authors, and an online poll among oncologists, 64% of whom were medical oncologists (119 out of 185).

They suggest the use of CanAssist Breast test in treatment decision algorithm.

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CanAssist Breast is an immunohistochemistry-based (IHC) test that quantifies protein expression levels of a combination of five unique nonproliferative biomarkers (CD44, Pan-Cadherin, N-Cadherin, ABCC4, and ABCC11). The data from the biomarker IHC testing are combined with three clinical parameters—tumor size (T), nodal status (N), and tumor grade—to generate a score for every patient. There are two risk categories—low and high.

The authors suggest that the test is developed and validated in Indians. They make a strong assertion that the CanAssist Breast is predictive for chemotherapy response. However, we were unable to find any study using CanAssist Breast that validated the predictive potential of the test in ascertaining with confidence that omitting chemotherapy for a patient with low-risk score would not impact the survival outcomes for the patient. Among all the various biomarker tests currently available, Oncotype DX and MammaPrint are found to be predictive for chemotherapy. All other tests including CanAssist Breast are prognostic tests that unravel the natural history of the disease.

We reviewed some of the published studies for CanAssist Breast that were referenced in the consensus document.^{7–10} These studies showed the test being prognostic for distant recurrences. However, all of these studies are retrospective in design. For now, we were unable to find any prospective phase 3 clinical trials for the test. It would also be ideal to have an independent group conduct such a study.

We also wish to highlight few other concerns regarding CanAssist Breast. First, unlike Oncotype DX and MammaPrint, CanAssist Breast is not an RNA-based assay. An IHC-based assay can be inferior to RNA-based assay in terms of reliability. For instance, Ki67 testing by IHC is generally considered prognostic and predictive. But it is also widely recognized that the test lacks reliability. There is substantial risk for interobserver variability. Second, it is also unclear if more weightage is given to the three clinical parameters (which is obtained from histopathological reporting) or the protein expression of five genes. If the former is the key factor, then how much does the test add value to the standard histopathological report. If the latter is the key factor, then the issue of reliability of IHC testing becomes crucial. Third, the cost of this assay is lower than the currently available predictive biomarker tests, but is still very much out of reach for the vast majority of patients in India.

Another limitation of the study pertains to the use of an online poll to develop consensus guidelines. It is certainly a good method for generating data in short duration. The small sample size, lack of an avenue for a discussion on pertinent questions, and the potential bias of selective framing of questions are some of them. In fact, in the study, almost 47% of oncologists were not convinced about the CanAssist Breast test and 41% stated that they will not avoid chemotherapy based on a low-risk score on the CanAssist Breast test. We believe that such an online survey-based study needs to be utilized as a template for further studies and discussions. Such studies could serve to highlight areas of need for research—including the one that is highlighted in this study—the need for a reliable,

indigenous predictive biomarker test for chemotherapy use in early-stage breast cancer.

In summary, while we wish there existed a biomarker test that is validated among Indians for predicting benefit or lack of benefit of adjuvant chemotherapy and was cost-effective, the available data suggest that CanAssist Breast is not there yet. We strongly feel that assisting the developers of this test platform to validate it in the context of a large prospectively and independently conducted phase 3 clinical trial must be a high priority for oncologists practicing in India.

As for practicing community oncologists in India and other LMICs, clinical judgement based upon patient and tumor-related factors still remains the best tool for decision-making. Shared decision-making with the patient and their family (where it matters)—which includes an assessment of the risk of recurrence, functional status, risk for chemotherapy and financial toxicity from therapy or testing—will probably go a long way in improving overall outcomes of our patients.

Conflicts of Interest

None to disclose.

References

- Mansour EG, Gray R, Shatila AH, et al. Survival advantage of adjuvant chemotherapy in high-risk node-negative breast cancer: ten-year analysis—an intergroup study. *J Clin Oncol* 1998;16(11):3486–3492
- Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365(9472):1687–1717
- Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004;351(27):2817–2826
- Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol* 2006;24(23):3726–3734
- Hoskins KF, Danciu OC, Ko NY, Calip GS. Association of race/ethnicity and the 21-gene recurrence score with breast cancer-specific mortality among US women. *JAMA Oncol* 2021;7(03):370–378
- Parikh PM, Bhattacharyya GS, Biswas G, et al. Practical Consensus Recommendations for Optimizing Risk versus Benefit of Chemotherapy in Patients with HR Positive Her2 Negative Early Breast Cancer in India. *South Asian J Cancer* 2021;10(04):213–219
- Attuluri AK, Serkad CPV, Gunda A, et al. Analytical validation of CanAssist-Breast: an immunohistochemistry based prognostic test for hormone receptor positive breast cancer patients. *BMC Cancer* 2019;19(01):249. Doi: 10.1186/s12885-019-5443-5
- Bakre MM, Ramkumar C, Attuluri AK, et al. Clinical validation of an immunohistochemistry-based CanAssist-Breast test for distant recurrence prediction in hormone receptor-positive breast cancer patients. *Cancer Med* 2019;8(04):1755–1764
- Sankaran S, Dikshit JB, Prakash Sv C, et al. CanAssist Breast impacting clinical treatment decisions in early-stage HR+ breast cancer patients: Indian Scenario. *Indian J Surg Oncol* 2021;12 (Suppl 1):21–29
- Patil P, Bakre MM, Basavaraj C, et al. Can Assist breast: an affordable breast cancer prognostic test validated on Asian patients. *J Clin Oncol* 2020;38(15, suppl):541–541