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Breast cancer
prognostic gene signature assay

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The Value of Gene Expression Prognostic Tests for Early-Stage Breast Cancer In Light of TAILORx Trial Results

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Advances in our understanding of the biology of breast cancer are guiding the development of individualized treatment plans, aiming to provide patients with the best chance for a cure while optimizing their quality of life.

When it comes to HR+ Her2- early-stage breast cancer management, one of the critical questions faced by physicians and patients is the choice of adjuvant treatment.

A number of gene expression signatures have been developed as prognostic markers in this setting including the 21 gene recurrence score, the 70 gene signature, the Prosigna® Risk of Recurrence (ROR) score, the EpClin score, and the Breast Cancer Index. All of these assays have been clinically validated for guiding the decision on adjuvant chemotherapy in node-negative tumors at low risk, with an excellent prognosis that would not warrant chemotherapy and their use has been endorsed by major treatment guidelines. With the recent publication of a comparison of leading gene expression signatures for prognosis, it has become clear that multiple gene expression signatures provide similar prognostic information[1].

Recently, results were reported from the large prospective TAILORx clinical trial evaluating the value of one of these signatures, the 21-gene assay (Oncotype DX®), regarding the appropriate treatment strategy for early-stage breast cancer patients within a specific range ("intermediate") of genomic risk scores (11-25)[2]. Previously, another objective of the same trial had already been reported demonstrating that a low recurrence score of 0 to 10 is associated with a low rate of distant recurrence when patients are treated with endocrine therapy alone[3].

An important question answered by the new TAILORx trial results is whether postmenopausal HR+ Her2- breast cancer patients classified as low to intermediate risk by a genomic test benefit from adjuvant chemotherapy treatment or not. The TAILORx study clearly demonstrated that postmenopausal patients with small tumors (median tumor size 1.5cm, IQR 1.2-2.0) that have not spread to any lymph nodes, in combination with a genomic recurrence score between 11 and 25 by Oncotype DX®, do not benefit from modern chemotherapy regimens compared to endocrine therapy alone with 7.5 years median follow-up.

We believe that the importance of these findings extends beyond the specific prognostic genomic assay used in the study. Together with the previously reported results of another large prospective study, the MINDACT trial[4], the results from TAILORx validate once again that evidence from prospective-retrospective studies categorized as Level 1b Evidence is well aligned with evidence from prospective studies (Level 1a Evidence) in the same clinical setting and is sufficient to guide clinical practice[5]. Therefore, both healthcare professionals and patients should be assured that the clinical value of Prosigna® based on its extensive and robust evidence base (three prospective-retrospective studies[6,7,8]) remains unchanged by the results from the TAILORx trial.

Although the TAILORx results provide an important contribution toward addressing some of our knowledge gap on how to manage a subset of patients with intermediate genomic scores, several important questions remained unanswered by the study results, specifically:

- The benefits of chemotherapy treatment in breast cancer patients who are clinically high risk with larger tumors (>2 cm) or positive lymph nodes (1-3 positive nodes)
- The benefits of chemotherapy treatment in postmenopausal women with a Oncotype DX® intermediate risk score of 26-30 as this group was not randomized in the trial
- The optimal duration of endocrine therapy which is another important treatment decision for HR+ Her2- early breast cancer patients
- The appropriate treatment strategy for pre-menopausal patients and whether the small benefit of chemotherapy can instead be accomplished by ovarian function suppression

The distinctive utility of Prosigna among the other tests has been clearly demonstrated by its robust evidence base. The TAILORx trial clearly highlights the importance of considering clinical factors such as menopausal status, nodal involvement, and tumor size for accurate risk prediction. Indeed, the nodal status and tumor size variables are included in the Prosigna algorithm to calculate the ROR score. In the TransATAC[1] study comparing six prognostic assays in a single cohort, Prosigna's risk of recurrence score provided the most prognostic information in node-negative patients. Further, in a real-world population-based study published in 2018[8], Prosigna demonstrated strong clinical utility in node-positive disease. In the study, 26% of the node-positive patients who were categorized as having a low-risk ROR score had a distant recurrence risk of <5% at 10 years. In addition, several studies have confirmed the ability of Prosigna to assess the risk of late distant recurrence[8,9,10] informing an important question regarding the duration of endocrine therapy.

In addition to the two already published prospective trials, TAILORx[2] and MINDACT[4], another prospective trial, OPTIMA[11], is currently ongoing. The OPTIMA trial is evaluating Prosigna's ability to predict which patients with high risk clinical factors (node-positive or tumor size greater than 3cm) will benefit from test-directed chemotherapy compared to standard chemotherapy. A preliminary study for the OPTIMA trial demonstrated that the revised Oncotype DX® cutoff of 25 is consistent with Prosigna's already established intermediate risk ROR cutoff of 60 from a prognostic perspective[12]. Results from the OPTIMA trial are expected to add to the body of evidence supporting Prosigna as a valid genomic tool to inform treatment management decisions in early-stage breast cancer.

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Prosigna® Breast Cancer Prognostic Gene Signature assay is 510(k) cleared by the US FDA for in vitro diagnostic use. The indications cleared by the FDA for this product are described in the package insert located at www.prosigna.com.

Prosigna® Breast Cancer Prognostic Gene Signature assay is not approved or cleared by the US FDA or any other regulatory agency to predict response to therapy, or to select the optimal therapy for patients.

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