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COMMENTARY

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The impact of 21-Gene Recurrence Score test and classic clinical-pathologic factors in guiding adjuvant therapy for HER-2 negative, ER-positive, early-stage breast cancer: A retrospective study

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Both adjuvant hormonal therapy (HT) and chemotherapy (CT) improve survival for women with early-stage breast cancer (ESBC) though recurrence risk reduction is small, and most patients do won't not benefit from CT it.[1] The 21-gene Oncotype DX Breast Recurrence Score® test (Oncotype DX, Genomic Health, Inc, Redwood City, CA) has been shown to predict responsiveness to adjuvant CT.[2] Recently published prospective studies demonstrated that patients with low Recurrence Score can safely forego adjuvant CT[3] leading to Oncotype DX's inclusion in multiple guidelines to aide treatment decisions. Whether physicians use these tests to influence decision-making is unclear. We examined whether Oncotype DX impacts adjuvant therapeutic decisions for HER-2-negative ESBC patients in Uruguay and whether Recurrence Score is associated with clinicopathological variables.

We identified 61 patients from a single, private-practice oncology clinic in Montevideo, Uruguay, from 2008 to 2014. Included criteria were axilla lymph node-negative ESBC, HER-2-negative, ER-positive, stage I or II breast cancer (BCa) and requested Oncotype DX prior to receiving adjuvant treatment.

After obtaining institutional review board approval, we abstracted demographic, medical history, tumor pathology, treatment recommendation pre-Oncotype DX, and treatment received post-Oncotype DX data. Patients without a recommendation pre-Oncotype DX were assigned a would-be treatment recommendation based on post-treatment, single-blind assessment of anonymized patient prognostic data.

Demographics, clinical characteristics, Recurrence Score distribution, and pre/post-Oncotype DX recommendations were described using descriptive statistics. Fisher's exact test was used to evaluate the correlation between tumor grade and categorized Recurrence Score (low < 18, intermediate = 18-30, and high ≥ 31). Linear regression tested the association between Recurrence Score and clinical variables. Two-tailed *P*-value ≤ .05 were considered significant.

Median age was 53 years (range: 28-84 years). Most patients were postmenopausal (54%), had grade II disease (66%), primary ductal histology (77%), moderate ER positivity (58%), pT1c cancers (61%), and low-risk Recurrence Score (69%). Median tumor size was 14 mm (range 4-30 mm). 22% had lymphovascular invasion. There were no significant associations between Recurrence Score and any risk factors except histologic grade ($P < .001$), though we found a significant association between higher grade and higher Recurrence Score.

Before receiving Oncotype DX, 21 patients (34%) were recommended to receive HT alone and 40 were recommended to receive HT + CT (66%). After Oncotype DX, HT was administered to 46 patients (75%), while HT + CT was administered to 15 (25%). Low Recurrence Scores were associated with low to no CT use, whereas high Recurrence Scores were associated with having CT. The Recurrence Score influenced treatment decision-making in 27 patients (44%) whose initial treatment recommendation changed after receiving Oncotype DX.

Oncotype DX evaluates BCa prognosis and estimates CT benefits among women with ESBC. Systematic decision-making for women with ESBC is unclear as treatments are often dictated by tumor subtype, when known, making it hard to determine when to use adjuvant CT + HT. We evaluated the association between Recurrence Score and ESBC risk factors, and whether use of Oncotype DX impacts treatment decisions among women with ESBC from a single-care center in Uruguay. We found no association between Recurrence

Score and any risk factor except tumor grade. Thus, Oncotype DX can impact treatment decisions, suggesting that this test provides unique information above and beyond pathology.

In our cohort, we showed that Recurrence Score influenced recommendations as treatment decisions changed in 44% of women. 37% of treatment recommendations remained after knowledge of the Recurrence Score in women originally recommended to undergo HT + CT; thus, 63% of women were spared treatments including CT. While our results are marginally higher than other studies,[4,5] these higher values may be reflective of higher perceived risk prior to Recurrence Score or higher histologic tumor grade (30% grade III vs 12%-19%, $P < .001$).[6,7]

Additionally, increasing Recurrence Scores were associated with increased likelihood of CT postassay. In our series, high Recurrence Score patients received HT + CT. Of the 9 patients recommended for HT + CT with intermediate scores, 6 exhibited several risk factors attributed with an increased risk of receiving a CT recommendation. A 2017 retrospective single-center study from Greece evaluated the impact of Oncotype DX testing on CT assignment among female ESBC patients and found that Recurrence Score was higher for cases with CT assignment ($P < .001$), which is consistent with our findings. Without the use of Oncotype DX, ~63% of their patients would have wrongly received CT and ~15% would have been assigned to the wrong treatment group.[8] Our study is consistent with previously published reports that use of the Recurrence Score can alter treatment recommendations in women with ESBC toward less aggressive regimens. Furthermore, like our findings, other studies have found that increasing Recurrence Score is positively correlated with increased use of CT.[9]

The largest randomized BCa trial to date, the Trial Assigning Individualized Options for Treatment (TAILORx), enrolled 10,273 subjects from 2006 to 2010 and used the Oncotype DX to determine whether HT alone had similar outcomes to HT + CT[10] among intermediate-risk women with HR-positive, HER2-negative, axillary lymph node-negative ESBC. In TAILORx, investigators defined Recurrence Score as low-risk (0-10), intermediate-risk (11-25), and high-risk (>26). Women classified as low-risk received HT, intermediate-risk were randomly assigned HT or HT + CT, and high-risk received HT + CT. Investigators found no difference between women who received HT and women who received CT ($P = .26$) when evaluating disease-free survival among women intended to be treated. Furthermore, investigators found HT + CT was not a better postsurgical treatment option than HT alone. These results confirm that use of the Recurrence Score can help physicians reduce treatment toxicity by providing accurate recommendations for intermediate-risk women for whom CT would provide no therapeutic benefit. With respect to our study, our charts and treatment decisions were made prior to the reporting of the TAILORx results and newly established Recurrence Score cut point of 25. Had results from TAILORx been available at the time of enrollment for our study, perhaps more patients would have been spared CT with potentially compromising outcomes, further supporting the need to include the use of the Recurrence Score in treatment decision-making.

Despite its clear strengths, such as providing context for the Oncotype DX test in a real patient population and being the second study in this population in South America, our study is not without limitations. One limitation is that the study used a single-center to sample patients. Further, patients were chosen by physician discretion for inclusion; that is, not all eligible patients at the single-center within the specified time period received Oncotype DX testing, only those patients who could self-pay since it is not covered by our health insurance system. Despite these limitations, we believe this study contributes to our knowledge about Uruguayan patients who requested Oncotype DX multigene assay. Furthermore, we showed that use of Oncotype DX helped a significant number of patients avoid CT. As such, use of the Oncotype DX test appears to influence physician recommendations regarding adjuvant treatment for women with ESBC.

Use of Oncotype DX can change decision-making for patients with ESBC and lead to a decrease in HT + CT overall. With further investigation, use of such tests may reduce indications of CT-based systemic therapies among women with BCa. More studies are required to determine how Oncotype DX influences treatment decisions in larger, more diverse populations.

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CONFLICT OF INTEREST

None.

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REFERENCES

1. Early Breast Cancer Trialists Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *The Lancet*. 2005;365:1687-1717.
2. Hyams DM, Schuur E, Angel Aristizabal J, et al. Selecting postoperative adjuvant systemic therapy for early stage breast cancer: a critical assessment of commercially available gene expression assays. *J Surg Oncol*. 2017;115:647-662.
3. Markopoulos C. Overview of the use of Oncotype DX((R)) as an additional treatment decision tool in early breast cancer. *Expert Rev Anticancer Ther*. 2013;13:179-194.
4. Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med*. 2015;373:2005-2014.
5. Gluz O, Nitz UA, Christgen M, et al. West German study group phase III PlanB trial: first prospective outcome data for the 21-gene recurrence score assay and concordance of prognostic markers by central and local pathology assessment. *J Clin Oncol*. 2016;34:2341-2349.
6. Lo SS, Mumby PB, Norton J, et al. Prospective multicenter study of the impact of the 21-gene recurrence score assay on medical oncologist and patient adjuvant breast cancer treatment selection. *J Clin Oncol*. 2010;28:1671-1676.

7. Bargallo JE, Lara F, Shaw-Dulin R, et al. A study of the impact of the 21-gene breast cancer assay on the use of adjuvant chemotherapy in women with breast cancer in a Mexican public hospital. *J Surg Oncol*. 2015;111:203-207.
8. Panousis D, Ntasiou P, Grosomanidis D, et al. Impact of oncotype DX on chemotherapy assignment: a retrospective single-center study on female breast cancer patients. *J BUON*. 2017;22:1199-1208.
9. Chen C, Dhanda R, Tseng WY, Forsyth M, Patt DA. Evaluating use characteristics for the oncotype dx 21-gene recurrence score and concordance with chemotherapy use in early-stage breast cancer. *J Oncol Pract*. 2013;9:182-187.
10. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med*. 2018;379:111-121.