Impact of Multigene Assays in Early Stage Breast Cancer

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There are a number of multigene assays that have been shown to reliably determine prognosis in patients with early-stage breast cancer [1–4]. However, only one test—the 21-gene recurrence score (RS) assay *oncotype DX*®—has been studied for use in predicting chemotherapy benefit among patients randomized in phase III studies of chemotherapy plus tamoxifen versus tamoxifen alone [1, 3, 4]. Thus, this test is commonly used by physicians to help determine which patients with early-stage, estrogen receptor–positive breast cancer should receive adjuvant cytotoxic chemotherapy to reduce the likelihood of recurrence and improve survival over and above the benefit from endocrine therapy alone. In the current issue of *The Oncologist*, Joh et al. [5] present the results of a retrospective study of the impact of this assay on physician decision making in the adjuvant treatment setting. Their results are consistent with other studies published on this topic to date—the RS assay does indeed impact physician decision making, and the frequency with which it does so is consistent across studies.

Two published prospective studies showed that the results of the RS assay changed the medical oncologist's adjuvant treatment recommendation pre- to post-RS assay result in 31.5% and 32% of cases, respectively [6, 7]. The majority of the changes were from chemotherapy plus hormone therapy to hormone therapy alone (22.5% and 21%) [6, 7]. A meta-analysis of nine studies, which also included seven retrospective studies, demonstrated a 36% overall rate of change in the treatment decision [8]. In patients for whom chemotherapy followed by hormone therapy was initially recommended, results of the RS assay led to 51% of cases being switched to a recommendation of hormone therapy alone. RS testing led to 13% of cases being switched from an initial recommendation of hormone therapy alone to chemotherapy followed by hormone therapy.

Although most of the studies included in this meta-analysis were from North American sites, the impact of the RS assay on decision making is also consistent on a global level. Similar results were reported in a U.K. study in which the initial treatment recommendation changed in 37.8% of cases [9], a German study

in which the initial treatment recommendation changed in 38.1% of cases [10], and a prospective Spanish study that showed a 32% rate of treatment recommendation change [6].

The retrospective study of Joh et al. [5] is an interesting addition to the other published retrospective studies on this topic in that it also evaluated the decision making of other breast specialists (breast surgeons and breast pathologists) in addition to medical oncologists. Physicians more frequently overestimated the recurrence risk when using traditional clinical–pathologic tumor features than when using the RS. The authors make the point that, based on clinical–pathologic features alone, patients could often be overtreated with chemotherapy because current studies indicate that patients with breast cancers of the biology reflected by a lower RS most likely gain little benefit from chemotherapy. It remains uncertain what the correct RS cutoff should be, below which chemotherapy could be omitted. The results of the recently closed intergroup Trial Assigning Individualized Options for treatment (Rx) [TAILORx], which randomized patients whose tumors had an RS of 11–25 to chemotherapy or not, are eagerly awaited to clarify the best adjuvant treatment approach for this group of women.

The authors appropriately comment on the limitations of their study. In addition to the points they raise, because the entire denominator of patients presenting to physicians was not included, some bias is perhaps introduced as reflected in the high percentage of cases with a low RS. Furthermore, it is not clear whether the physicians participating in this investigation used tools such as Adjuvant! Online to formulate the pre-RS risk determination, or whether a proliferation index such as Ki-67 was routinely available.

In this study, the authors found that the RS significantly correlated with tumor grade, mitotic activity, lymphovascular invasion, hormone receptor status and human epidermal growth factor receptor 2/neu status, factors routinely found on a standard pathology report. They allude to an as-yet-unpublished algorithm by their group to predict an RS accurately. In

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deed, a number of studies are under way globally to develop predictive tools for use when multigene assays such as onco^{type} DX[®] are not available or cannot be afforded [11–13]. These algorithms require validation in phase III studies with an endocrine therapy alone control arm. Then, users need to apply rigid quality control, especially for those algorithms dominated by immunohistochemical scoring of multiple single genes, because most of the studies reported to date employed central laboratories with expert breast pathologists. In particular, algorithms that provide chemotherapy prediction data note the dominant contribution of a proliferation index, with cutpoints not yet standardized [14]. Overall, it should be noted that cost savings from obtaining the RS assay and basing treatment choices on that result rather than clinical–pathologic variables alone have been demonstrated in North American, European, and Asian countries [15–19].

This study, together with all others published to date, documents that the 21-gene RS assay does impact physician adjuvant treatment decision making, and does so in a similar magnitude worldwide. The randomized, ongoing Microarray In Node negative Disease may Avoid ChemoTherapy [MINDACT] study will inform the question of survival outcome when selecting therapy based on clinical–pathologic factors versus results of a multigene assay. However, it appears that the best predictive tools of the future for chemotherapy benefit will most likely combine clinical–pathologic and multigene variables in one algorithm [1, 20]. Until these new tools are validated, use of the 21-gene RS assay for treatment decision making remains a valid and useful option for many patients and their physicians.

AUTHOR CONTRIBUTIONS

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REFERENCES

1. Sotiriou C, Pusztai L. Gene-expression signatures in breast cancer. *N Engl J Med* 2009;360:790–800.
2. Albain KS, Paik S, van't Veer L. Prediction of adjuvant chemotherapy benefit in endocrine responsive, early breast cancer using multigene assays. *Breast* 2009;18(suppl 3):S141–S145.
3. 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;24:3726–3734.
4. Albain KS, Barlow WE, Shak S et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: A retrospective analysis of a randomised trial. *Lancet Oncol* 2010;11:55–65.
5. Joh JE, Esposito NN, Kiluk JV et al. The effect of Oncotype DX[®] recurrence score on treatment recommendations for patients with estrogen receptor positive early stage breast cancer and correlation with estimation of recurrence risk by breast cancer specialists. *The Oncologist* 2011;16:1520–1526.
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. Albanell J, Gonzalez A, Borrego MR et al. Prospective transGEICAM study of the impact of the 21-gene recurrence score assay and traditional clinicopathological factors on adjuvant clinical decision making in women with estrogen receptor-positive (ER+) node-negative breast cancer. *Ann Oncol* 2011 Jun 6 [Epub ahead of print].
8. Hornberger JC, Chien R. Meta-analysis of the decision impact of the 21-gene breast cancer Recurrence Score in clinical practice [abstract P201]. Presented at the 2011 St. Gallen Oncology Conference, St. Gallen, Switzerland, March 16–19, 2011.
9. Holt ADH, Bertelli G, Pudney D et al. Results from a prospective clinical study on the impact of onco^{type} DX[®] on adjuvant treatment decision and risk classification by Nottingham prognostic index (NPI) and recurrence score (RS) [abstract P196]. Presented at the 2011 St. Gallen Oncology Conference, St. Gallen, Switzerland, March 16–19, 2011.
10. Blohmer JU, Ataseven B, Kuhn T et al. German multicentre decision impact study of onco^{type} DX[®] recurrence score (RS) on adjuvant treatment in estrogen receptor positive (ER+) node negative (N0) and node positive (N+) early breast cancer [abstract P206]. Presented at the 2011 St. Gallen Oncology Conference, St. Gallen, Switzerland, March 16–19, 2011.
11. Cuzick J, Dowsett M, Wale C et al. Prognostic value of a combined ER, PgR, Ki67, HER2 immunohistochemical (IHC4) score and comparison with the GHI recurrence score—results from transATAC. *Cancer Res* 2009;69(24 suppl):74.
12. Flanagan MB, Dabbs DJ, Brufsky AM et al. Histopathologic variables predict onco^{type} DX[®] recurrence score. *Mod Pathol* 2008;21:1255–1261.
13. Geradts J, Bean SM, Bentley RC et al. The onco^{type} DX[®] recurrence score is Correlated with a composite index including routinely reported pathobiologic features. *Cancer Invest* 2010;28:969–977.
14. Goldhirsch A, Wood WC, Coates AS et al. Strategies for subtypes—dealing with the diversity of breast cancer: Highlights of the St Gallen International Expert Consensus on the Primary Therapy of
- Early Breast Cancer 201. *Ann Oncol* 2011;22:1736–1747.
15. Hassan S, Mittmann N. A cost benefit analysis of the 21-gene breast cancer assay within a Canadian health care system [abstract 6111]. Presented at the 2011 American Society of Clinical Oncology Annual Meeting, Chicago, Illinois, June 4–8, 2011.
16. Madaras B, Pozsa P, Gerencser Z et al. Evaluation of the cost-effectiveness of onco^{type} DX[®] multigene assay in Hungary [abstract P215B]. Presented at the 2011 St. Gallen Oncology Conference, St. Gallen, Switzerland, March 16–19, 2011.
17. Liaropoulos L, Galanis P, Kaitelidou D et al. Gross financial evaluation of the application of the 21-gene assay onco^{type} DX[®] for adjuvant chemotherapy decision-making in estrogen receptor-positive node negative breast cancer in Greece [abstract P202]. Presented at the 2011 St. Gallen Oncology Conference, St. Gallen, Switzerland, March 16–19, 2011.
18. De Lima Lopes G, Chien R, Hornberger JC. Cost-benefit analysis of a 21-gene recurrence score for early stage breast cancer in Singapore [abstract P215A]. Presented at the 2011 St. Gallen Oncology Conference, St. Gallen, Switzerland, March 16–19, 2011.
19. Lyman GH, Cosler LE, Kuderer NM et al. Impact of a 21-gene RT-PCR assay on treatment decisions in early-stage breast cancer: An economic analysis based on prognostic and predictive validation studies. *Cancer* 2007;109:1011–1018.
20. Tang G, Shak S, Paik S et al. Comparison of the prognostic and predictive utilities of the 21-gene recurrence score assay and Adjuvant! for women with node-negative, ER-positive breast cancer: Results from NSABP B-14 and NSABP B-20. *Breast Cancer Res Treat* 2011;127: 133–142.

EDITOR'S NOTE: See the accompanying article, “The effect of Oncotype DX recurrence score on treatment recommendations for patients with estrogen receptor positive early stage breast cancer and correlation with estimation of recurrence risk by breast cancer specialists,” by J.E. Joh, N.N. Esposito, J.V. Kiluk, et al., on pages 1520–1526 of this issue.