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Prediction of benefit from chemotherapy in ER-positive/HER2-negative breast cancer—a problem still to be solved

The majority of the panelists of the 2013 St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer supported the view that the 21-gene Recurrence Score (RS) of Genomic Health, Inc. is providing not only prognostic, but also predictive information regarding the utility of cytotoxic therapy for patients with luminal disease [1]. This is a puzzling statement as, only a few lines below in this publication, the authors of the consensus document acknowledge that such information on luminal tumors has been derived from clinical trials encompassing HER2-positive patients. There is no comment on this obvious disaccord.

The claim of the RS having predictive power to identify a benefit from chemotherapy for breast cancer patients is based on information derived from two independent clinical trials (NSABP-B20 and SWOG-8814). In the NSABP-B20 trial, patients had been randomized to either receive tamoxifen alone or in combination with (C)MF chemotherapy [2]. Patients classified as high risk by the RS appeared to benefit from adding (C)MF to tamoxifen treatment while the low- and intermediate-risk patients did not. The trial also included patients with HER2-positive tumors in a non-published proportion. HER2-positive tumors have a high absolute risk of recurrence. Correspondingly, the absolute benefit patients with such tumors derive from chemotherapy treatment is high [3]. HER2 is also one of the genes measured in the RS. Therefore, the compelling results obtained for the RS in the NSAPB-B20 trial may be partially due to the inclusion of HER2-positive tumors and may thus not be representative for its performance in the subgroup of ER-positive/HER2-negative tumors. Using this investigation to make conclusions on luminal tumors may thus be misleading. Also, the analysis of the NSABP-B20 cohort suffers from a methodological weakness not uncommon in early gene expression analysis studies: samples from the tamoxifen-only arm of the NSABP-B20 study had already been used in the definition of the RS. Accordingly, the published NSABP-B20 data do not meet the standards of an independent validation for the RS. In order to clarify if (C)MF really confers a benefit in the RS-high-risk group of the NSABP-B20 trial, the analysis should be repeated, excluding all HER2-positive tumors and all samples that had been initially used for training the RS.

The interaction between RS and chemotherapy benefit was also analyzed in patients from the SWOG-8814 trial. This trial had investigated the value of adding CAF to tamoxifen [4]. The results demonstrated that the RS is able to predict a benefit from chemotherapy in the entire cohort, including 12% of tumors positive by HER2-RNA assay. Still, the benefit from chemotherapy was not analyzed in the clinically relevant subgroup of ER-positive/HER2-negative breast cancer patients. Again, we suggest repeating the analysis to obtain an unequivocal result for luminal tumors.

We conclude that neither the RS nor any other currently used gene expression test has demonstrated its ability to predict a benefit from chemotherapy treatment in patients with ER-positive/HER2-negative tumors. Nevertheless, validated gene expression tests providing information incremental to established risk factors continue to be a valuable tool to identify patients with low risk of recurrence having low absolute benefit from chemotherapy.

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disclosure

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