Viewpoint
Show me the genes – I will tell you who/how to treat!
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During the 1990s, mortality from breast cancer finally began to decline. This has been the result of a series of factors, such as widespread screening and education (with consequent early detection), new diagnostic techniques and crucial therapeutic developments, particularly in the area of new drugs. Notwithstanding these important advances, metastatic breast cancer remains a virtually incurable disease. The results of clinical trials and meta-analyses have led to recommendations that some form of adjuvant systemic therapy be administered to the great majority of patients with breast cancer. The decision regarding which specific therapy is given is based on tumour and patient characteristics, but it is mainly empirical because it extrapolates to the individual conclusions drawn by studies conducted at the population level, leading to inefficient treatment of many in order to benefit a few. Accurate risk assessment and the ability to predict both sensitivity and tolerability to treatments in each individual patient have therefore became major goals and challenges for the oncology community. The advent of microarray technology and its potential clinical applications is an important step toward tailored treatment.

The recently published study from the National Surgical Adjuvant Breast and Bowel Project (NSABP) group lead by Paik [1], in collaboration with Genomic Health Inc., represents a landmark trial in this field. Using quantitative RT-PCR, these researchers developed a recurrence score based on 21 genes that appears to predict accurately the likelihood of distant recurrence in tamoxifen-treated patients with node-negative, oestrogen receptor (ER)-positive breast cancer. Initially, this predictor was designed to be a general prognostic tool, developed in a mixed population of patients receiving chemotherapy and tamoxifen. Following a literature search of the most important microarray experiments relating to breast cancer prognosis, 250 candidate genes were selected. Of these, 21 genes were chosen and the recurrence score developed by analyzing the results of these genes in three independent preliminary studies involving 447 patients [2–4]. The selection of the final 16 cancer-related genes was based primarily on the strength of their performance in all three studies and the consistency of primer or probe performance in the assay. Cutoff points were chosen based on the results of NSABP trial B-20, and allowed for the classification of patients into three risk categories: low risk (recurrence score <18), intermediate risk (recurrence score ≥18 and <31), and high risk (recurrence score ≥31).

The report published in the *New England Journal of Medicine* [1] describes the retrospective validation of this multigene predictor in 675 archival samples from node-negative, ER-positive breast cancer patients, treated with adjuvant tamoxifen in the NSABP B-14 trial. Fifty-one per cent of patients were classified as low risk, with a rate of distant recurrence at 10 years of 6.8%, and 27% patients were classified as high risk, with a rate of distant recurrence at 10 years of 30.5%; this difference was statistically significant ($P < 0.001$). The recurrence score was also significantly correlated with the relapse-free interval and overall survival ($P < 0.001$ for both). Notably, this predictive power was independent of age and tumour size ($P < 0.001$). The recurrence score also provided significant information beyond tumour grade, despite the low levels of concordance in assessment of grade between the three pathologists in the study (43% overall).

There are additional important messages with potential clinical implications. First, not all patients with small (<1 cm) tumours were at low risk, because the recurrence score classified 40% of these patients as intermediate or high risk, with a 15–20% risk of distant recurrence at 10 years. Second, the subgroup of patients with moderately differentiated tumours (the most common grade) could be delineated into low-risk and high-risk groups using the recurrence score.

As in all retrospective studies, bias in patient selection are inevitable, and some relatively odd characteristics of the patient population were the low rate of HER2 positivity

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AI = aromatase inhibitor; ER = oestrogen receptor; NSABP = National Surgical Adjuvant Breast and Bowel Project; RT-PCR = reverse transcription polymerase chain reaction.

(8.2%) and the absence of correlation between the levels of ER or progesterone receptor proteins and the risk of recurrence.

Because recurrence in the ipsilateral breast, local recurrence, and regional recurrence were not considered events or censoring events, this score should not be used to predict locoregional relapses but only distant relapses. More importantly, and unlike the 70-gene profiler developed by the Amsterdam group [5,6], the NSABP recurrence score does not have pure prognostic value but rather predictive value regarding response to tamoxifen. A study performed by the MD Anderson group [7] provides support for this; in that study there was absence of correlation between the score and rate of distant recurrence in 149 selected patients with node-negative breast cancer who did not receive adjuvant systemic therapy. Notably, and despite the difference between the two systems stated above, the percentage of patients classified as low risk with the NSABP score is similar to the one found with the 70-gene profiler of the Amsterdam group, and is considerably higher than the percentage of patients classed as low risk by classical clinicopathological criteria.

Genome-wide studies have confirmed the existence of clinically suspected subgroups of ER-positive breast cancers with distinct outcomes and responses to therapy. Aromatase inhibitors (AIs) are a newer class of endocrine agents that have been found to be superior to tamoxifen in the metastatic setting and recently also in the adjuvant setting. These new agents are considerably more expensive and are not without side effects, namely osteoporosis and cardiovascular events. The role of sequential administration of tamoxifen and an AI in comparison with use of an AI alone remains to be determined. A 'biological identifier' of tamoxifen resistance could help to determine the patient population in which alternative endocrine strategies and/or cytotoxic therapies are clearly needed. The Oncotype™ multigene predictor was able to identify a group of patients with a rate of distant recurrence at 10 years of 30.5% − a risk similar to that observed among node-positive breast cancer patients − despite treatment with tamoxifen, which indicates a clear need for more effective therapies in this group of patients.

More recently, the NSABP group has taken this work further by analyzing the predictive potential of the Oncotype™ predictor with respect to adjuvant chemotherapy [8]. In this clinical study, 2299 node-negative, ER-positive breast cancer patients were randomly assigned to receive tamoxifen alone or chemotherapy (either CMF [cyclophosphamide, methotrexate and 5-fluorouracil] or MF [methotrexate and 5-fluorouracil]) followed by tamoxifen. Only 651 patients were evaluable for the recurrence score substudy, mostly because of uncollected blocks. Nevertheless, this subpopulation had similar characteristics

to the clinical population as a whole. Although there was overall benefit from adding chemotherapy in these patients ($P = 0.02$), when the Oncotype™ predictor was applied it became apparent that this benefit was restricted to the high risk patients (distant relapse-free survival 88% versus 60%; $P = 0.001$); no benefit was seen in the low and intermediate risk patients (distant relapse-free survival 90% versus 89%; $P = 0.71$). The interaction test between gene expression and chemotherapy was significant at 0.0368, which indicates that the recurrence score could identify those patients who clearly benefitted from the addition of chemotherapy to adjuvant tamoxifen.

Despite its commercial availability in the USA, the Oncotype™ multigene predictor should not yet be used in clinical practice because it has not yet passed a crucial phase of its validation − a well designed and adequately powered prospective study. Such a trial is in advanced stages of planning by the US Intergroup, and will incorporate this new tool into treatment decision making in node-negative, endocrine responsive patients. This trial is along the same lines as the work of the European TRANSBIG (an international translational research network linked to the Breast International Group) consortium, which is prospectively validating the 70-gene Amsterdam profiler in the large multicentre MINDACT (Microarray in Node Negative Disease May Avoid Chemotherapy) trial.

Only this type of international and multidisciplinary collaboration will allow the incorporation of new technologies and/or biological hypotheses into clinical trials, facilitating their clinical implementation and transforming the dream of individualized treatment into reality.

Competing interests
The author(s) declare that they have no competing interests.

References
1. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, Baehner FL, Walker MG, Watson D, Park T, *et al.*: **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004, **351:**2817-2826.
2. Esteban J, Baker J, Cronin M, Liu M-L, Llamas MG, Walker MG, Mena R, Shak S: **Tumor gene expression and prognosis in breast cancer: multi-gene RT-PCR assay of paraffin-embedded tissue [abstract].** *Prog Proc Am Soc Clin Oncol* 2003, **22:**850.
3. Cobleigh MA, Bitterman P, Baker J, Cronin M, Liu M-L, Borchik R, Tabesh B, Mosquera J-M, Walker MG, Shak S: **Tumor gene expression predicts distant disease-free survival (DDFS) in breast cancer patients with 10 or more positive nodes: high throughout RT-PCR assay of paraffin-embedded tumor tissues [abstract].** *Prog Proc Am Soc Clin Oncol* 2003, **22:**850.
4. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, Baehner R, Walker M, Watson D, Park T, Bryant J, Wolmark N: **Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients: NSABP studies B-20 and B-14 [abstract].** *Breast Cancer Res Treat* 2003, **82:**A16.
5. van 't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M, Peterse HL, van der Kooy K, Marton MJ, Witteveen AT, *et al.*: **Gene expression profiling predicts clinical outcome of breast cancer.** *Nature* 2002, **415:**530-536.
6. van de Vijver MJ, He YD, van't Veer LJ, Dai H, Hart AA, Voskuil DW, Schreiber GJ, Peterse JL, Roberts C, Marton MJ, *et al.*: **A**

gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med* 2002, **347:**1999-2009.

7. Esteva FJ, Sahin AA, Coombes K, Baker J, Cronin M, Walker M, Watson D, Cristofanilli M, Shak S, Hortobagyi GN: **Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients: MD Anderson Clinical Validation Study [abstract].** *Breast Cancer Res Treat* 2003, **82:**A16.

8. Paik S, Shak S, Tang G, Kim C, Joo H, Baker J, Cronin M, Watson D, Bryant J, Costantino J, Wolmark N: **Expression of the 21 genes in the recurrence score assay and prediction of clinical benefit from tamoxifen in NSABP B-14 and chemotherapy in NSABP B-20 [abstract 24].** *Breast Cancer Res Treat* 2004, **88:**S15.