Patient profiling in breast cancer —is knowledge power?

The idea that it is acceptable to diagnose a patient with 'breast cancer' is outdated. It has long been recognized that breast cancer is not a single disease entity but constitutes different subtypes that are based on varying clinicopathological features and can also be defined by gene-expression profiling. It is important to identify the correct intrinsic subtype so clinicians can offer optimal therapy. But, how much profiling is helpful and where should we be drawing the line in terms of accuracy, cost and the acquisition of knowledge?

As a prototypical example, when considering using the HER2-targeted agent trastuzumab it is important to identify the HER2 status of patients with breast cancer to determine if they should be receiving the drug. This is particularly true because patients with HER2-positive disease have a poor prognosis without treatment, but trastuzumab is associated with cardiotoxicity and high cost so treating HER2-negative patients with this drug is not an acceptable option. So, in HER2 we have an ideal easily identifiable target with an associated therapy option—or do we?

Current guidelines recommend the use of immunohistochemical (IHC) analysis or fluorescence *in situ* hybridization (FISH) to determine the level of HER2 expression. However, there are limitations to both of these methods. Inter-laboratory variation means that some tumors would be identified as HER2 positive by one pathologist, and HER2 negative by another. Whether other techniques, such as reverse transcription PCR might offer an alternative, more reliable, technique (or supplement IHC and FISH) is still under question—as discussed in this issue (Ignatiadis, M. & Sotiriou, C. *Nat. Rev. Clin. Oncol.* **9**, 12–14; 2012).

In addition to HER2 status, the most-important molecular profile for patients with breast cancer is their hormone receptor status, in particular estrogen receptor (ER) status. The advent of prognostic gene-expression profiles for breast cancer has shown that the most-important prognostic indicator is the ER status of the tumor. Patients with ER-negative disease have a poor prognosis, which is confirmed in the prognostic results of both the currently FDA-approved gene-expression profiles, Onco*type* DX® and MammaPrint®. Patients with ER-negative disease should almost uniformly be offered adjuvant chemotherapy to improve their chances of a long recurrence-free survival. It is doubtful, at this stage, whether there is any value in determining the gene-expression profiles of patients with ER-negative disease other than for research purposes as they should be treated with the same strategy independent of any other genetic information that can be obtained (other than HER2 status as described previously).

In patients with ER-positive disease, the prognosis is less straight forward and it is in these patients that the benefit of specialized gene-expression profiles is likely to be the most significant. For patients who are classified as being low risk by either of the two approved gene-expression profiles, and who are also determined to be node negative, it is likely that they can safely be spared further systemic treatment. For those patients who are identified to have high-risk disease, systemic treatment and careful monitoring are indicated.

Thus, gene-expression profiles are an additional tool in the decision-making process that can enable clinicians to supplement the information they have obtained from the pathology of the disease to make the best, informed decisions possible. These assays do have limitations though. An area where questions exist is for patients who are classified by the profiles to be at an intermediate risk of relapse; clinical trials are ongoing in this patient population to determine what their profile should mean in terms of recommended treatment options.

As is probably clear from this editorial, the use of gene-expression profiles in patients with breast cancer is not a simple case of 'useful for all patients' or 'no use at all'. As we frequently experience in the oncology field, the situation is more complex than that. This complexity is reflected in two articles in this issue (Prat, A. *et al. Nat. Rev. Clin. Oncol.* **9**, 48–57; 2012 and Weigelt, B. *et al. Nat. Rev. Clin. Oncol.* **9**, 58–64; 2012) that discuss the use of gene-expression profiles in patients with breast cancer, and that come to different conclusions in terms of their utility.

Where there does not seem to be any controversy is that the clinicopathological features of breast tumors are independent prognostic indicators that can and are used by clinicians worldwide to determine the optimal therapy for their patients. Furthermore, the use of freely available resources, such as Adjuvant! Online, can help determine patient prognosis and aid decision making. To help decide how best to spend budgets that are limited worldwide, it is important going forward to determine which patients the current gene-expression assays will benefit most. It is hoped that the results of TAILORx and MINDACT might shed some light on this issue, despite not being designed with this question in mind. In the meantime, until new tests and information are available, we will have to make our own judgements.

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Competing interests
The authors declare no competing interests.