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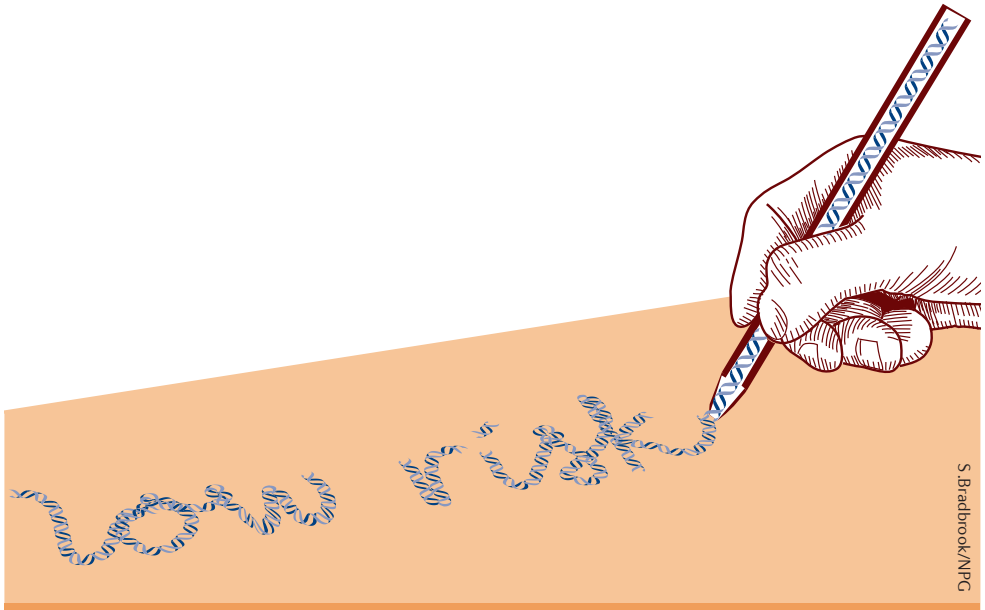

S.Bradbrook/NPG

BREAST CANCER

Genetic signature might spare 100,000 women annually from chemotherapy

Adjuvant chemotherapy can benefit a subset of patients with early stage breast cancer, and is typically allocated to those deemed to be at a high clinical risk of distant metastasis. This risk can be determined using various algorithms incorporating disease characteristics (such as intrinsic molecular subtype, tumour grade and size, and lymph-node status), and patient characteristics (for example, age, menopausal status, and performance status). Now, results from the MINDACT study indicate that tumour gene-expression profiling can further refine the use of chemotherapy, and might reduce overtreatment.

The phase III MINDACT study was designed to evaluate the clinical utility of a 70-gene signature (MammaPrint) in improving the selection of patients for adjuvant chemotherapy. The MammaPrint test was used to predict the genetic risk of distant recurrence for 6,693 women with early stage breast cancer and 0–3 positive lymph nodes, while clinical risk was estimated using the Adjuvant! Online algorithm. Of these women, 1,550 (23.2%) had disparate clinical and genetic risk results (low clinical and high genetic risk, or high clinical and low genetic risk) and were randomly assigned (1:1) to receive chemotherapy or no chemotherapy. Patients deemed at a high genetic and clinical risk all received chemotherapy, whereas none of those with a low genetic and clinical risk were treated with chemotherapy.

The MINDACT results demonstrate that women with a high clinical risk and a low genetic risk who did not receive chemotherapy had a 5-year survival without distant metastasis of 94.7%. Moreover, the absolute difference in this outcome between the groups of women with a high clinical risk and low genetic risk who did and did not receive chemotherapy was only 1.5% ($P = 0.27$).

"46% of patients with early stage breast cancer identified as being at a high risk of recurrence according to clinicopathological factors, and who would, therefore, usually be candidates for adjuvant chemotherapy, were reclassified as low risk using MammaPrint; the MINDACT results show that these patients do not benefit from chemotherapy," explains Laura van't Veer, who was involved in the trial. She adds: "MammaPrint could change clinical practice by providing critical prognostic information to aid in assessing the risk of distant metastasis, and could potentially spare more than 100,000 women annually worldwide from unnecessary toxicities and costs associated with chemotherapy."

> "this trial confirms the clinical value of the 70-gene signature in identifying... patients who can safely forego adjuvant chemotherapy"

The majority of patients included in the trial (88.4%) had hormone-receptor-positive disease, and these patients comprised 98.1% of the high clinical and low genomic risk group. Lajos Pusztai, who was not involved in the study, thus opines that "this trial confirms the clinical value of the 70-gene signature in identifying hormone-receptor-positive patients who can safely forego adjuvant chemotherapy." He stresses, however, that "it is very important to recognize which patient populations the results might not apply to." For example, "the number of $HER2^+$ patients was relatively low, and to what extent this test could be used to spare $ER^+/HER2^+$ patients from chemotherapy remains uncertain."

Pusztai highlights two additional important points. "First, the MINDACT data indicate that patients who are deemed clinically low risk do not benefit from MammaPrint testing: only 18% of these patients were reclassified as high risk using the 70-gene test and, most importantly, chemotherapy did not improve their outcome." This group had a 5-year distant-metastasis-free survival with and without chemotherapy of 95.8% versus 95.0% ($P = 0.66$). "Second, virtually all patients with triple-negative breast cancers (96%) had a high genomic risk; therefore, the test is not useful in this patient population."

David Killock

ORIGINAL ARTICLE Cardoso, F. *et al.* 70-gene signature as an aid to treatment decisions in early-stage breast cancer. *N. Engl. J. Med.* **375**, 717–729 (2016)