Genetic Test Identifies Breast Cancer Patients Who May Avoid Chemotherapy

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The management of early-stage, hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer often involves adjuvant chemotherapy, despite its associated toxicities and potential for overtreatment in a significant proportion of patients. The clinical dilemma lies in accurately identifying which patients will derive a meaningful benefit from chemotherapy versus those who can achieve comparable outcomes with endocrine therapy alone. A validated multigene expression assay provides a tool to stratify risk and guide treatment decisions, potentially sparing many patients from unnecessary chemotherapy exposure.

KEY TAKEAWAYS

- The Pivot: A multigene expression assay can identify patients with HR+/HER2- early breast cancer who have a low risk of recurrence and may safely omit adjuvant chemotherapy.
- The Data: In a large prospective trial, patients with a low recurrence score (RS) who received endocrine therapy alone had a 9-year distant recurrence rate of approximately 1.6%.
- The Action: Clinicians should consider using validated multigene expression assays to inform adjuvant chemotherapy decisions in eligible patients with HR+/HER2- early breast cancer, particularly those with intermediate clinical risk.

Adjuvant chemotherapy for early-stage, hormone receptor-positive, HER2-negative breast cancer has been a cornerstone of treatment for decades, aiming to reduce the risk of distant recurrence and improve overall survival. However, the benefits of chemotherapy are not uniform across all patients, and its administration carries substantial acute and long-term toxicities, including myelosuppression, nausea, fatigue, alopecia, cardiotoxicity, and secondary malignancies. Identifying patients who are unlikely to benefit from chemotherapy, and thus can be spared these adverse effects, represents a significant clinical need. Traditional clinicopathological factors, such as tumour size, nodal status, and histological grade, provide some prognostic information, but their ability to predict chemotherapy benefit is limited. This has led to the development and integration of molecular assays into clinical practice to refine risk stratification and guide adjuvant treatment decisions.

The underlying principle of these molecular assays is to quantify the expression of specific genes within the tumour tissue, providing a more granular assessment of tumour biology and its aggressive potential than conventional pathological features alone. By analysing the expression patterns of a predefined set of genes, these assays generate a recurrence score (RS) or similar prognostic index. A low RS indicates a tumour with a favourable biological profile and a low likelihood of distant recurrence, suggesting that the incremental benefit from chemotherapy may be minimal or non-existent.

Conversely, a high RS indicates a more aggressive tumour, where chemotherapy is more likely to provide a substantial benefit. The challenge has been to establish clear thresholds for these scores and to validate their utility in large, prospective clinical trials to ensure that patients are not undertreated by omitting chemotherapy.

The Role of Multigene Expression Assays in Treatment De-escalation

One such multigene expression assay, the 21-gene recurrence score (Oncotype DX Breast Recurrence Score), has been extensively studied and is widely used in clinical practice. This assay analyses the expression of 21 genes (16 cancer-related genes and 5 reference genes) from formalin-fixed, paraffin-embedded tumour tissue. It generates a score ranging from 0 to 100, which correlates with the likelihood of distant recurrence at 10 years and the magnitude of chemotherapy benefit in HR+, HER2- early breast cancer. The assay was initially validated in retrospective analyses of archived tumour samples from large clinical trials, demonstrating its prognostic utility and its ability to predict chemotherapy benefit. These early studies established that patients with a low RS (typically 0-10) had an excellent prognosis with endocrine therapy alone, while those with a high RS (typically >25) derived significant benefit from adjuvant chemotherapy.

The critical question, however, remained for patients with an intermediate RS (typically 11-25), who represent a substantial proportion of HR+, HER2- breast cancer cases. For these patients, the decision regarding adjuvant chemotherapy was often ambiguous, leading to variability in clinical practice and potential overtreatment. To address this, large prospective trials were initiated to definitively determine whether chemotherapy could be safely omitted in patients with an intermediate RS, particularly those with node-negative disease. These trials aimed to provide high-level evidence to support treatment de-escalation based on the molecular profile of the tumour, thereby reducing chemotherapy exposure and its associated morbidity without compromising oncological outcomes.

One pivotal study, the TAILORx trial, enrolled 10,273 women with HR+, HER2- early breast cancer, with tumours that were node-negative or had micrometastases. Patients were stratified based on their 21-gene recurrence score. Those with a recurrence score of 0-10 received endocrine therapy alone. Patients with a recurrence score of 26-100 received chemoendocrine therapy. The primary objective of the trial focused on the intermediate-risk group (recurrence score 11-25), where patients were randomised to receive either endocrine therapy alone or chemoendocrine therapy. The primary endpoint was invasive disease-free survival (IDFS). The trial demonstrated that in the overall population of patients with an intermediate recurrence score, endocrine therapy alone was non-inferior to chemoendocrine therapy for IDFS. Specifically, the 9-year IDFS rates were 83.3% for endocrine therapy alone and 84.3% for chemoendocrine therapy (HR for recurrence or death, 1.08; 95% CI, 0.94 to 1.24; P=.29). This finding indicated that chemotherapy could be safely omitted for the majority of patients in the intermediate-risk group.

Further detailed analyses from the TAILORx trial revealed important nuances within the intermediate-risk group. For women 50 years of age or younger with a recurrence score of 16-25, there was a modest but statistically significant benefit from chemotherapy. In this subgroup, the 9-year IDFS was 83.8% with chemoendocrine therapy versus 80.2% with endocrine therapy alone (HR, 0.79; 95% CI, 0.63 to 0.99). This suggests that age and recurrence score interact, and younger patients with higher intermediate scores may still derive some benefit from chemotherapy. However, for women older than 50 years with a recurrence score of 11-25, and for all women with a recurrence score of 11-15, chemotherapy provided no additional benefit. The 9-year distant recurrence rate in the low-risk group (RS 0-10) who received endocrine therapy alone was remarkably low at 1.6%, confirming that these patients can confidently forgo chemotherapy. These

data provide robust evidence to guide personalised treatment decisions, moving away from a one-size-fits-all approach.
Another significant trial, RxPONDER, investigated the utility of the 21-gene recurrence score in patients with HR+, HER2- breast cancer and 1-3 positive lymph nodes. This trial enrolled 5,083 patients, randomising those with an intermediate recurrence score (0-25) to either endocrine therapy alone or chemoendocrine therapy. The primary endpoint was invasive disease-free survival. The results showed that in postmenopausal women with 1-3 positive lymph nodes and an intermediate recurrence score (0-25), endocrine therapy alone was non-inferior to chemoendocrine therapy. The 5-year IDFS rates were 91.6% for endocrine therapy alone and 91.7% for chemoendocrine therapy (HR for IDFS, 1.03; 95% CI, 0.83 to 1.28). This finding extended the utility of the recurrence score to a population with nodal involvement, further supporting chemotherapy de-escalation in postmenopausal women with intermediate-risk, node-positive disease.
However, similar to TAILORx, a benefit from chemotherapy was observed in premenopausal women with 1-3 positive lymph nodes and an intermediate recurrence score, with a 5-year IDFS of 89.0% for chemoendocrine therapy versus 84.7% for endocrine therapy alone (HR, 0.60; 95% CI, 0.43 to 0.83). This highlights the importance of considering menopausal status in addition to the recurrence score when making treatment decisions for node-positive patients.
The widespread adoption of these multigene expression assays has led to a significant reduction in chemotherapy use for patients with early-stage HR+, HER2- breast cancer. By accurately identifying patients with a low risk of recurrence, these tests enable clinicians to tailor treatment plans, avoiding the unnecessary toxicities and costs associated with chemotherapy. This de-escalation of treatment not only improves patient quality of life but also optimises healthcare resource allocation. The evidence from these large prospective trials has been instrumental in integrating these assays into major clinical guidelines, including those from the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN), which now recommend their use to guide adjuvant chemotherapy decisions in eligible patients.
Despite the substantial progress, limitations and areas for further research remain. The assays are primarily validated for HR+, HER2- breast cancer, and their utility in other breast cancer subtypes is less established. While the 21-gene recurrence score is widely used, other multigene assays, such as MammaPrint (70-gene signature) and Prosigna (50-gene signature), also exist and provide similar prognostic information, though with different gene sets and scoring systems. Comparative effectiveness studies between these different assays are ongoing to determine if one offers superior predictive or prognostic value in specific patient populations. Furthermore, the precise biological mechanisms underlying the differential chemotherapy benefit in younger versus older patients, and in premenopausal versus postmenopausal women, warrant further investigation. Understanding these mechanisms could lead to the development of even more refined predictive biomarkers and targeted therapies. The integration of these molecular assays with other emerging technologies, such as circulating tumour DNA (ctDNA) analysis, may further enhance risk stratification and treatment monitoring in the future, offering even greater precision in oncology care.

> **CLINICAL IMPLICATIONS**
> The data from trials like TAILORx and RxPONDER represent a significant step forward in personalising breast cancer treatment. For too long, a substantial proportion of patients with early-stage HR+, HER2- breast cancer received adjuvant chemotherapy with minimal or no benefit, enduring considerable toxicity. The ability of the 21-gene recurrence score to reliably identify patients who can safely forgo chemotherapy, particularly those

with node-negative disease and postmenopausal women with 1-3 positive nodes, is a clear win for patient quality of life and healthcare efficiency. Clinicians should be confident in de-escalating treatment for these low-risk groups, adhering to the evidence-based guidelines that now incorporate these molecular assays. However, the nuances revealed by these trials, specifically the benefit of chemotherapy in younger patients and premenopausal women with intermediate recurrence scores, underscore the complexity of treatment decisions. It is not a simple binary choice based solely on the recurrence score. Age, menopausal status, and nodal involvement must be integrated into the decision-making process. This requires careful patient counselling, ensuring that the risks and benefits of chemotherapy are thoroughly discussed, especially in these borderline cases where a modest benefit may exist. The pharmaceutical industry, while not directly impacted by a reduction in chemotherapy sales for these specific patient groups, should focus on developing more precise predictive biomarkers for other breast cancer subtypes and refining existing assays to further delineate chemotherapy benefit in the remaining ambiguous populations.

From a broader perspective, the success of these genetic tests highlights the increasing importance of molecular diagnostics in oncology. Payers and healthcare systems should ensure equitable access to these validated assays, as their use leads to more appropriate treatment, reduced healthcare costs associated with unnecessary chemotherapy administration and management of its side effects, and improved patient outcomes. The ongoing research into other multigene assays and the integration of novel biomarkers will continue to refine our understanding of tumour biology, moving us closer to truly individualised cancer care. This evolution demands continuous education for clinicians to keep pace with the rapidly advancing field of precision oncology.

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