Are we closer to being able to select patients with node-positive hormone receptor-positive breast cancer who can safely omit chemotherapy?

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Abstract: The treatment of hormone receptor-positive, HER2-negative breast cancer has become increasingly individualized, thanks to the development of genomic testing. Gene expression assays provide clinicians and patients with both prognostic and predictive information regarding breast cancer recurrence risk and potential benefit of chemotherapy. While the ability to tailor therapy based on clinicopathologic and genomic factors has enabled a growing number of women to forego chemotherapy, several questions remain regarding how best to apply genomic assay results across varying subgroups of women. Here, we review the role of genomic assays for patients with both lymph node-negative and lymph node-positive breast cancer, and how these assays may help us more precisely select patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) breast cancer with or without lymph node involvement who can safely omit chemotherapy in the future.

Keywords: aromatase inhibitor, breast cancer, hormone receptor-positive breast cancer, molecular testing, neoadjuvant therapy

Introduction
Hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) is the most common subtype of breast cancer, accounting for over half of all breast cancer cases in the United States. Treatment for women with early-stage HR+, HER2− disease has been revolutionized in recent years, thanks to advances in genomic testing. Gene expression profiles, including the 21-gene Recurrence Score® (RS) assay (Oncotype DX®) and 70-gene signature MammaPrint assay, evaluate patterns of gene expression within tumor samples to determine risk of recurrence following surgery and are being utilized to determine the potential benefit of chemotherapy. As chemotherapy is associated with significant risk of toxicity, there has been significant interest in better understanding the heterogeneity among risk groups to determine the number of women for whom the benefit of chemotherapy outweighs the risk.

Gene expression assays in HR+, lymph node-negative breast cancer
The application of gene expression profiles was first evaluated among women with HR+, HER2− breast cancer without lymph node involvement. Initially validated in prospective-retrospective National Surgical Adjuvant Breast and Bowel Project (NSABP) data, RS was found to discriminate 10-year rates of distant recurrence in low-, intermediate- and high-risk groups. Participants with high RS (>26) clearly derived benefit from chemotherapy, while those with low RS (<10) did not. The prospective Microarray in Node-Negative and 1–3 Positive Lymph Node Disease May Avoid Chemotherapy study (MINDACT) noted similar findings utilizing the 70-gene signature MammaPrint assay to classify patients as low or high risk, concluding that genomically low-risk patients may be able to safely avoid chemotherapy.
The Trial Assigning Individualized Options for Treatment (TAILORx) validated the clinical utility of the 21-gene RS assay and addressed lingering questions regarding chemotherapy benefit for women with intermediate RS (11–25), a category encompassing the vast majority of women with HR+, HER2− breast cancer.6 Study participants with intermediate RS 11–25 were randomized to receive adjuvant endocrine therapy or chemotherapy followed by endocrine therapy. Results confirmed that there was no additional benefit for chemotherapy in women over age 50 years; however, for women 50 years old or younger, benefit from adjuvant chemotherapy was noted in the subgroup of women with RS greater than or equal to 16.6 In a subsequent prospective trial, Sparano et al.7 combined clinical risk assessment, based on tumor size and histologic grade, with 21-gene RS to determine rate of recurrence among nearly 9500 women with HR+, HER2−, N0 breast cancer. Clinical risk was found to be prognostic of distant recurrence for women with intermediate RS (11–25) or high RS (26–100). High clinical risk was defined as tumors >1 cm in diameter with high histologic grade, >2 cm and intermediate grade or >3 cm and low grade. Notably, among women 50 years of age or younger with low RS (0–10) who received endocrine therapy alone, estimated rate of distance recurrence at 9 years was less than 5% (≤1.8 ± 0.9%) regardless of the clinical risk group. Estimated recurrence remained low at 4.7% ± 1.0% for women with intermediate RS and low clinical risk. In contrast, young women with high clinical risk demonstrated recurrence rates of 12.3 ± 2.4% for women with intermediate RS receiving endocrine therapy alone and 15.2 ± 3.3% for those with high RS who received chemotherapy followed by endocrine therapy.7 Furthermore, the estimated absolute benefit of chemotherapy among premenopausal women was stratified by clinical risk and noted similar benefit among women with RS 21–25, regardless of the clinical risk group (6.4 ± 4.9% low clinical risk versus 8.7 ± 6.2% in high clinical risk group). In contrast, women with intermediate RS 16–20 and low clinical risk did not benefit from chemotherapy (~0.2 ± 2.1%), whereas those in the high clinical risk group were shown to have a 6.5 ± 4.9% absolute benefit.7 Overall, these findings dramatically decreased the number of women with HR+ breast cancer for whom adjuvant chemotherapy is absolutely recommended. Results from TAILORx and antecedent data have shifted the discussion surrounding treatment for women with lymph node-negative breast cancer and have undoubtedly provided patients and providers alike with confidence in recommendations to forego chemotherapy in patients unlikely to benefit.

**Gene expression assays in HR+, lymph node-positive breast cancer**

While genomic tests have been well validated for women with breast cancer without lymph node involvement, their utility in predicting recurrence risk and resulting chemotherapy benefit for women with lymph node-positive disease has remained unclear. Given that one-third of patients with early-stage HR+, HER2− breast cancer are found to have lymph node involvement at the time of presentation, determining the optimal course of treatment for this subgroup has been of utmost importance.1,8 Early data from the SWOG S8814 trial challenged the existing standard of treatment with adjuvant chemotherapy for all women with HR+, lymph node-positive breast cancer.9,10 Findings from this retrospective analysis of tumor tissue from postmenopausal women with HR+, HER2− breast cancer with lymph node involvement suggested that RS had a predictive role in determining the benefit of chemotherapy in the lymph node-positive population. Notably, patients in the low RS group (RS <18) had no added survival benefit from chemotherapy, whereas patients falling into the high RS subset (RS ≥31) showed significant improvement in disease-free survival (DFS) with chemotherapy and endocrine therapy versus endocrine therapy alone. Participants with N1 breast cancer represented 61.9% of this retrospective analysis, and the 5-year DFS was 91% for those with N1 breast cancer and an RS ≤25. In the first 5 years, RS-by-treatment interaction was significant for DFS (p = 0.03). This survival benefit in the high RS group was independent of the number of lymph nodes involved.9

Other exploratory analyses echoed similar findings among subsets of lymph node-positive patients, adding strength to the hypothesis that certain subgroups within the HR+, HER2− lymph node-positive cohort may be able to safely avoid chemotherapy.11,12 The MINDACT study randomized patients with discordant clinical and genomic risk profiles based on the MammaPrint 70-gene signature to receive chemotherapy or not.13 Patients with low clinical and genomic risk did not receive chemotherapy, whereas patients with concordant high-risk profiles did receive...
MammaPrint assay importantly suggested that HER2−, N1 breast cancer.15 In this prospective study, 5-year DFS among patients with RS ≤11 who received endocrine therapy alone was noted to be similar in pN0 (94.2%, 90.4–98.0%) and pN1 (94.4%, 89.5–99.3%) subgroups.14 Together, these findings justified the omission of chemotherapy for a significant percentage of women with HR+, HER2− breast cancer with 1–3 lymph nodes involved.

The first results of the long-awaited RxPONDER trial have now been reported for patients with HR+, HER2−, N1 breast cancer.15 In this prospective trial, participants with 1–3 positive axillary lymph nodes and RS ≤25 were randomized to endocrine therapy alone versus chemotherapy followed by endocrine therapy, with the primary objective of determining the effect of chemotherapy on invasive disease-free survival (IDFS) and its relationship to RS. While outcomes did not demonstrate a statistically significant improvement in 5-year IDFS for the entire cohort of women, with 58% of the expected 832 events reported, important differences based on menopausal status were noted. Among the 67% of women who were postmenopausal, there was no demonstrated benefit from chemotherapy, with 5-year IDFS rates of 91.9% versus 91.3% for endocrine therapy and chemotherapy groups, respectively [hazard ratio (HR) = 1.02, 95% CI: 0.82–1.26, p = 0.89].15 In contrast, premenopausal women were shown to benefit significantly from chemotherapy, with 5-year IDFS rates of 89% in the endocrine therapy group versus 93.9% in the chemotherapy arm (HR = 0.60, 95% CI: 0.43–0.83, p = 0.002). This benefit persisted in the premenopausal group with regard to distant disease-free survival (DDFS) (HR = 0.58, 95% CI: 0.39–0.87, p = 0.009). Overall, RxPONDER data showed RS to be prognostic, but not predictive of chemotherapy benefit, that is, the relative benefit from chemotherapy also increases with higher RS. Although relative chemotherapy benefit for premenopausal women did not increase concomitantly with RS for participants with RS 0–25, there was greater absolute IDFS noted for premenopausal participants with higher RS who received chemotherapy.15

Assay application in premenopausal women

These data establishing that postmenopausal women with HR+, N1 breast cancer can safely forego chemotherapy serve as significant progress in individualizing risk and minimizing unnecessary chemotherapy exposure. While this greatly reduces the percentage of postmenopausal women who will require chemotherapy, it raises further considerations with regard to the premenopausal population. The 40% relative improvement in IDFS and 42% improvement in DDFS in premenopausal women noted in RxPONDER highlights existing questions regarding the underlying drivers of chemotherapy benefit in this population.15

The question of whether chemotherapy benefit for premenopausal women is attributed to direct cytotoxic effects or rather, from the indirect effect of ovarian function suppression, remains unanswered. It is important to note that among premenopausal women evaluated in RxPONDER, 12.7% had ovarian function suppression within 12 months of randomization (6.3% in the chemotherapy group and 19% in endocrine-only group), while 36.6% of the endocrine-only group who were 40 years of age or younger received ovarian suppression.15 Chemotherapy-induced amenorrhea, occurring in approximately 40% of women who receive chemotherapy, has been associated with improvements in recurrence rates and in overall survival (OS).16–20 The Tamoxifen and Exemestane Trial (TEXT) and Suppression of Ovarian Function Trial (SOFT) studies evaluated 4891 women with HR+, HER2− breast cancer who received chemotherapy and demonstrated a 5% improvement in recurrence rates for women...
who received ovarian function suppression in addition to standard endocrine therapy, noting up to 10% absolute improvement in 8-year freedom from recurrence in those who received ovarian function suppression in conjunction with aromatase inhibitor use specifically.\textsuperscript{21} The participants who benefited most were those who received chemotherapy, likely because of their higher risk of recurrence. Similar findings were noted in the NSABP B-30 trial, which demonstrated improvements in both OS (relative risk: 0.76, \( p = 0.04 \)) and DFS (relative risk: 0.70, \( p < 0.001 \)) among premenopausal women who experienced chemotherapy-induced amenorrhea for at least 6 months following adjuvant chemotherapy.\textsuperscript{22} Notably, these improved outcomes associated with ovarian function suppression were noted, regardless of treatment received (sequential-ACT, concurrent-ACT or docorubicin-docetaxel).\textsuperscript{22} While the mechanism of action of chemotherapy in premenopausal women is certainly multifactorial, further studies are needed to better understand which subsets of women may derive equal or potentially more benefit from ovarian function suppression rather than chemotherapy.

**Remaining questions in HR-positive, lymph node-positive breast cancer**

Despite the recent advances in therapeutic approaches to women with HR+, HER2− breast cancer with lymph node involvement, there is still much to learn. In the West German Study Group Adjuvant Dynamic Marker-Adjusted Personalized Therapy (ADAPT) trial, women with HR+ breast cancer and RS 12–25 were given a brief course of neoadjuvant endocrine therapy (tamoxifen or AI), followed by repeat evaluation of Ki67. Patients who demonstrated a positive response to endocrine therapy, defined as a drop in Ki67 below 10%, remained on endocrine therapy.\textsuperscript{23} These patients were shown to have excellent 5-year IDFS rates of 92.6% (95% CI: 90.8–94.0%), similar to the RS 0–11 group (93.9%, 95% CI: 91.8–95.4%).\textsuperscript{23} In addition, both RS groups exhibited similar rates of DDFS and overall survival on endocrine therapy alone, approaching 96% and 98%, respectively.\textsuperscript{23} Notably, approximately one-third of the women in this cohort were premenopausal and one-fourth had N1 disease.

Prospective data from the Optimal Personalized Treatment of Early Breast Cancer Using Multiparameter Analysis (OPTIMA) study may provide further insight into patients with node-positive breast cancer.\textsuperscript{24} In this multicenter study, women and men aged 40 years or older with early-stage HR+, HER2− breast cancer with 1–9 axillary lymph nodes involved (or tumor size of \( \geq 30 \) mm if lymph node-negative) will be randomized to standard treatment with chemotherapy followed by endocrine therapy or to undergo Prosigna testing; in the Prosigna testing arm, patients with a high score (\( > 60 \)) will receive standard treatment (chemotherapy followed by endocrine therapy), whereas patients will receive endocrine therapy alone if the 50-gene Prosigna score is found to be low. These awaited data will provide further clarification surrounding the use of endocrine therapy in this high-risk cohort.

While a genomic test can be helpful for understanding the underlying biology, considering clinical risk can help further individualize risk and systemic therapy decision-making with patients. Developed utilizing information from NSABP B-14 and TAILORx trials, the RSClin tool combines genomic information from Oncotype RS with clinicopathologic factors to determine 10-year estimate of recurrence risk and chemotherapy benefit.\textsuperscript{6,25,26} This model, designed for women with HR+, lymph node-negative breast cancer, was demonstrated to provide more prognostic information than either RS or clinicopathologic features alone (\( p < 0.001 \)).\textsuperscript{26} Further advances in integrative tools like RSClin will assist providers in striking the ideal balance of weighing genomic risk factors with clinicopathologic features in treatment decision-making, including with node-positive disease.

**Intra-assay comparison**

Finally, when it comes to head-to-head comparison of genomic assays, data remain limited. Oncotype DX and MammaPrint remain the two most commonly used genomic assays, each with prospective validation from TAILORx, RxPONDER and MINADCT, respectively.\textsuperscript{13,15} The 21-gene assay and 70-gene signature assay have often been used in combination, with the later providing clinicians with more actionable information in cases of clinically ambiguous RS.\textsuperscript{27} Initially validated to assess relapse risk in postmenopausal women with early-stage, HR+ breast cancer with up to three positive lymph nodes after 5 years of endocrine therapy, newer data have confirmed that the Prosigna assay has prognostic value for women across age groups and menopausal status.\textsuperscript{28,29} Similarly, the IHC-4 score provides
accurate prognostic information for predicting risk of distant metastasis for postmenopausal women with early-stage, HR+ breast cancer utilizing quantitative immunohistochemistry values of estrogen receptor, progesterone receptor, HER2 and Ki67 in combination with other clinicopathologic variables.\textsuperscript{30,31} Retrospective comparison of the prognostic value for distant recurrence of six gene expression signatures used in The Translational Study of Anastrozole or Tamoxifen Alone or Combined (TransATAC) cohort identified important differences in prognostic performance with regard to timing of recurrence.\textsuperscript{32} The Breast Cancer Index (BCI), Prosigna assay (ROR) and EndoPredict (EPclin) were all shown to more accurately predict late recurrence (5–10 years) than RS, IHC-4, or Clinical Treatment Score (CTI). Importantly, combined clinical and genomic models were shown to have enhanced performance with regard to patients with 1–3 positive lymph nodes.\textsuperscript{32} The feasibility phase of OPTIMA, the OPTIMA prelim study, was designed to evaluate concordance between genomic testing. While the amount of information gleaned from Oncotype DX, MammaPrint, Prosigna (PAM50), NexCourse Breast (IHC4-AQUA) and IHC4 was compared and demonstrated to be broadly equivalent, there was significant discordance of 60% with regard to predicted risk stratification and subtype classification.\textsuperscript{33,34} Ongoing research is needed to further clarify the prognostic and predictive power of these assays in HR+/HER2− breast cancer, particularly regarding risk of late recurrence.

Conclusion
As we move further into the era of precision medicine and individualized risk assessment, our ability to tailor therapies for patients continues to improve. Genomic risk assessment has enabled countless women and their providers to make more informed choices with regard to breast cancer treatment, the result of which has enabled a growing number of women to forego chemotherapy and its potential toxicities. While there is certainly more work to be done to optimize the precision of risk assessment and its application to treatment choice, we are closer to being able to select patients with HR+, HER2− breast cancer with or without lymph node involvement who can safely omit chemotherapy.

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