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Clinical and genomic risk to guide the use of adjuvant therapy for breast cancer

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Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer


BACKGROUND
The use of adjuvant chemotherapy in patients with breast cancer may be guided by clinicopathological factors and a score based on a 21-gene assay to determine the risk of recurrence. Whether the level of clinical risk of breast cancer recurrence adds prognostic information to the recurrence score is not known.

METHODS
We performed a prospective trial involving 9427 women with hormone-receptor–positive, human epidermal growth factor receptor 2–negative, axillary node–negative breast cancer, in whom an assay of 21 genes had been performed, and we classified the clinical risk of recurrence of breast cancer as low or high on the basis of the tumor size and histologic grade. The effect of clinical risk was evaluated by calculating hazard ratios for distant recurrence with the use of Cox proportional-hazards models. The initial endocrine therapy was tamoxifen alone in the majority of the premenopausal women who were 50 years of age or younger.

RESULTS
The level of clinical risk was prognostic of distant recurrence in women with an intermediate 21-gene recurrence score of 11 to 25 (on a scale of 0 to 100, with higher scores indicating a worse prognosis or a greater potential benefit from chemotherapy) who were randomly assigned to endocrine therapy (hazard ratio for the comparison of high vs. low clinical risk, 2.73; 95% confidence interval [CI], 1.93 to 3.87) or to chemotherapy plus endocrine (chemoendocrine) therapy (hazard ratio, 2.41; 95% CI, 1.66 to 3.48) and in women with a high recurrence score (a score of 26 to 100), all of whom were assigned to chemoendocrine therapy (hazard ratio, 3.17; 95% CI, 1.94 to 5.19). Among women who were 50 years of age or younger who had received endocrine therapy alone, the estimated (±SE) rate of distant recurrence at 9 years was less than 5% (≤1.8±0.9%) with a low recurrence score (a score of 0 to 10), irrespective of clinical risk, and 4.7±1.0% with an intermediate recurrence score and low clinical risk. In this age group, the estimated distant recurrence at 9 years exceeded 10% among women with a high clinical risk and an intermediate recurrence score who received endocrine therapy alone (12.3±2.4%) and among those with a high recurrence score who received chemoendocrine therapy (15.2±3.3%).

CONCLUSIONS
Clinical-risk stratification provided prognostic information that, when added to the 21-gene recurrence score, could be used to identify premenopausal women who could benefit from more effective therapy. (Funded by the National Cancer Institute and others; ClinicalTrials.gov number, NCT00310180.)
CLINICOPATHOLOGICAL FEATURES, including tumor size, histologic grade, and the presence of axillary lymph-node metastases, provide prognostic information about disease recurrence in women who have localized breast cancer after surgery, but these features have not been shown to be predictive of benefit from adjuvant chemotherapy. In women with hormone-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative early breast cancer, the 21-gene recurrence-score assay provides prognostic information that is independent of clinicopathological features, and a high score (on a scale of 0 to 100) indicates a higher rate of distant recurrence and is predictive of chemotherapy benefit. A high score has been defined as 31 or higher on the basis of the prospective validation National Surgical Adjuvant Breast and Bowel Project (NSABP) B20 and Southwest Oncology Group S8814 trial cohorts or 26 or higher on the basis of the NSABP B20 trial cohort.

The prospective Trial Assigning Individualized Options for Treatment (TAILORx) showed that endocrine therapy alone was noninferior to adjuvant chemotherapy plus endocrine (chemoendocrine) therapy in women with hormone-receptor–positive, HER2-negative, axillary node–negative breast cancer and a 21-gene recurrence score of 11 to 25. An exploratory analysis indicated some benefit of chemotherapy in women 50 years of age or younger who had a recurrence score of 16 to 25. The trial also showed a low percentage of women with distant recurrence (3%) at 9 years with endocrine therapy alone if the recurrence score was 0 to 15, irrespective of age.

Here, we report the results of secondary analyses of the TAILORx trial that were designed to determine whether clinical risk, as assessed with the use of an algorithm that integrates tumor size and histologic grade, adds prognostic information to the 21-gene recurrence score and predictive information regarding the benefit of chemotherapy. We further examined the relationship between age and the absolute chemotherapy benefit in women who were 50 years of age or younger and had a recurrence score of 16 to 25.

METHODS

TRIAL DESIGN AND PATIENTS

TAILORx, a prospective clinical trial, was sponsored by the National Cancer Institute and was coordinated by the Eastern Cooperative Oncology Group–American College of Radiology Imaging Network (ECOG-ACRIN) Cancer Research Group, as previously described. Women who participated in the trial provided written informed consent, including a statement of willingness to have treatment assigned or randomly assigned on the basis of the 21-gene Oncotype DX recurrence-score assay performed in a central laboratory.

OBJECTIVE AND DEFINITION OF CLINICAL RISK

The standardized definitions for efficacy end points (STEEP) criteria were used for end-point definitions. One end point was the distant recurrence–free interval, referred to here as distant recurrence (defined as the time from registration to the date of distant recurrence of breast cancer, or of death with distant recurrence, if death was the first manifestation of distant recurrence). Another end point was invasive disease–free survival, defined as the time from registration to the first event of recurrence (distant or locoregional), second primary cancer (excluding nonmelanoma skin cancers), or death without evidence of recurrence.

A prespecified secondary trial objective was to determine whether clinical risk, as assessed with the use of the Adjuvant! algorithm, added information regarding prognosis for recurrence and prediction of chemotherapy benefit to that projected by the Oncotype DX test. Classic pathologic information and outcome results were also used to refine models based on classic information and genomic tests. Adjuvant! is a tool that uses clinicopathological characteristics to provide estimates of breast cancer outcomes at 10 years on the basis of the Surveillance, Epidemiology, and End Results registry data and treatment effects associated with adjuvant chemotherapy and endocrine therapy derived by the Early Breast Cancer Trialists’ Collaborative Group meta-analysis that has been validated in several data sets.

Since Adjuvant! is no longer available for clinical use, we assessed the prognostic information provided by a binary clinical-risk categorization based on the Adjuvant! algorithm as used in the MINDACT (Microarray in Node-Negative Disease May Avoid Chemotherapy) trial. A low clinical risk was defined as the probability of breast cancer–specific survival at 10 years without systemic therapy among more than 92% of women.
Clinical and Genomic Risk in Breast Cancer with Estrogen Receptor–Positive Tumors who Received Endocrine Therapy Alone, as Projected by Adjuvant! (Version 8.0).1 Clinical risk was defined as low if the tumor was 3 cm in diameter or smaller and had a low histologic grade, 2 cm or smaller and had an intermediate grade, or 1 cm or smaller and had a high grade; the clinical risk was defined as high if the low-risk criteria were not met.

**Oversight**

This trial was coordinated by the ECOG-ACRIN Cancer Research Group, with other federally funded groups participating, including the Southwest Oncology Group, the Alliance for Clinical Trials in Oncology, NRG Oncology, and the Canadian Cancer Clinical Trials Network.

The statistical analysis was performed by the second author, the manuscript was written by the first author, and a final version of the manuscript, incorporating changes recommended by the coauthors, was reviewed and approved by all the authors, who vouch for the accuracy and completeness of the data and the adherence of the trial to the protocol (available with the full text of this article at NEJM.org). No one who is not an author contributed to the manuscript. No commercial support was provided in the planning or execution of the trial, but commercial support was provided by Genomic Health, the makers of the 21-gene risk score tool, for collection of follow-up information from the treatment sites.

**Statistical Analysis**

This analysis involved the same intention-to-treat population previously described.7 Event-free rates were estimated with the use of the Kaplan–Meier method, with confidence intervals computed with log–log transformation and Greenwood’s variance. Hazard ratios were estimated with the use of partial likelihood analysis of the Cox proportional-hazards model, with confidence intervals symmetric on the log-ratio scale. No corrections for multiple comparisons were made.

**Results**

**Clinical-Risk Category, 21-Gene Recurrence Score, and Age**

The trial was conducted from April 2006 to October 2010. Of the 9719 women in the trial who were included in the primary intention-to-treat population and who had data that could be evaluated, information regarding clinical risk, including both tumor size and histologic grade, was available for 9427 (97.0%), of whom 6615 (70.2%) had low clinical risk and 2812 (29.8%) had high clinical risk, with a similar distribution according to age (≤50 years vs. >50 years). The recurrence score was high (a score of 26 to 100) in 589 patients (8.9%) with low clinical risk and in 770 patients (27.4%) with high clinical risk; these distributions were also similar according to age. Endocrine therapy administered to women who were reported to be premenopausal at registration and to have a recurrence score of 11 or higher included tamoxifen in 78% of the women (including 35% who crossed over to an aromatase inhibitor) and ovarian function suppression alone or in combination with an aromatase inhibitor in 13%; 7% of the women were reported to receive an aromatase inhibitor, which could indicate either incorrect reporting of menopausal status at registration or chemotherapy-induced menopause.

**Clinical-Risk Category and Prognosis**

Prognostic information provided by the clinical-risk category is shown in Figure 1. Estimated hazard ratios reflect the comparison of the high clinical-risk group with the low clinical-risk group; a hazard ratio greater than 1 indicated that a high clinical risk was prognostic for a higher event rate. The clinical-risk category added prognostic information regarding distant recurrence in patients who received endocrine therapy alone and who had an intermediate recurrence score of 11 to 25 (hazard ratio, 2.73; 95% confidence interval [CI], 1.93 to 3.87) and in patients treated with chemoendocrine therapy who had an intermediate recurrence score (hazard ratio, 2.41; 95% CI, 1.66 to 3.48) or a high recurrence score of 26 to 100 (hazard ratio, 3.17; 95% CI, 1.94 to 5.19).

In a model of distant recurrence incorporating clinical risk and the recurrence score for the group of patients with an intermediate recurrence score (6496 patients and 240 distant recurrences), significant prognostic information was provided by both the clinical-risk level (hazard ratio for high vs. low risk, 2.42; P<0.001) and the continuous recurrence score (hazard ratio for an increase of 1 point in the recurrence score, 1.08;
P<0.001). Similar findings were noted for rates of invasive disease–free survival events (defined as freedom from invasive disease recurrence, second primary cancer, or death).

An evaluation of the effect of clinical risk on prognosis with respect to distant recurrence and invasive disease–free survival, stratified according to age, showed similar prognostic effects in women older than 50 years of age and in women 50 years of age or younger. Weaker associations between clinical risk and distant recurrence were observed in older women who had a low recurrence score (a score of 0 to 10) than among those who had a higher recurrence score, and no association was observed in younger women with a low recurrence score, which may be explained at least partly by the lower event rate among younger women and the smaller sample size.

Clinical Risk Category and Chemotherapy Benefit

Estimated treatment hazard ratios for 6496 women with an intermediate recurrence score who were randomly assigned to endocrine or chemoendocrine therapy are shown in Figure 2. An estimated hazard ratio of greater than 1 indicates a higher recurrence rate with endocrine therapy alone than with chemoendocrine therapy. The level of clinical risk was not predictive of chemotherapy benefit in women who had an intermediate recurrence score in the entire population, nor in the 4353 women who were older than 50 years of age or the 2143 women who were 50 years of age or younger (Fig. 2A). Trends suggested a chemotherapy benefit in 476 women who were younger than 50 years of age and had a recurrence score of 21 to 25, but these trends did not vary according to clinical risk (Fig. 2B).
We further evaluated chemotherapy benefit as a function of age and menopausal status in 4338 women with a recurrence score of 16 to 25 (Fig. 3). We found that a chemotherapy benefit was most evident at 45 years of age in premenopausal women and waned at younger and older ages and with menopause, consistent with an effect due to chemotherapy-induced premature menopause. Similar results were found when age (without menopausal status) was evaluated as a continuous variable with the use of a natural spline (Fig. S1 in the Supplementary Appendix, available at NEJM.org).
The New England Journal of Medicine

Event Rates at 9 Years, Stratified According to Age

Kaplan–Meier estimates of event rates at 9 years, stratified according to age, are shown in Table 1. In 6469 women who were older than 50 years of age (two thirds of the trial population), the mean (±SE) distant recurrence rate at 9 years was similar, irrespective of use or nonuse of chemotherapy, in the cohort with an intermediate recurrence score, regardless of whether the clinical risk was low (4.0±0.7% vs. 3.5±0.6%) or high (8.3±1.5% vs. 9.3±1.9%). Similar findings were noted with respect to invasive disease–free survival.

In 2958 women who were 50 years of age or younger (one third of the trial population), use or nonuse of chemotherapy in the group with an intermediate recurrence score was associated with similar distant recurrence rates at 9 years if the clinical risk was low (3.9±1.0% and 4.7±1.0%, respectively), but distant recurrence rates were lower with the use of chemotherapy in the group with high clinical-risk (6.1±1.8% and 12.3±2.4%, respectively). Rates of distant recurrence at 9 years were very low among patients who were 50 years of age or younger who had a low recurrence score, irrespective of clinical-risk category (≤1.8±0.9%).

Owing to fewer second primary cancers and deaths, rates of invasive disease–free survival events were lower among younger women across all recurrence-score groups than among women who were older than 50 years of age. The level of clinical risk also added prognostic information with regard to distant recurrence in the 1359 women (both younger and older women) with a high recurrence score who received chemoendocrine therapy. Distant recurrence rates were also low among 589 women with a high recurrence score and low clinical risk who received chemotherapy (7.0±2.4% among older women and...
6.2±2.5% among younger women) and were similar to those among older women with a low recurrence score and high clinical risk (7.4±3.4%) who received endocrine therapy alone. In contrast, among 770 women with a high recurrence score and high clinical risk, distant recurrence rates were high among both older and younger women despite the use of chemotherapy (19.8±3.9% and 15.2±3.3%, respectively).

**Table 1. Distant or Locoregional Disease Recurrence, Second Primary Cancer, or Death, and Distant Recurrence at 9 Years, According to Use or Nonuse of Adjuvant Chemotherapy, Stratified According to Age, Recurrence Score, and Clinical Risk (Intention-to-Treat Population).**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clinical Risk</th>
<th>No. of Patients</th>
<th>Estimated Probability of Recurrence, Second Primary Cancer, or Death (95% CI)†</th>
<th>Hazard Ratio for Recurrence, Second Primary Cancer, or Death (95% CI)†</th>
<th>Estimated Probability of Distant Recurrence (95% CI)†</th>
<th>Hazard Ratio for Distant Recurrence (95% CI)†</th>
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<td><strong>Patients &gt;50 yr</strong></td>
<td></td>
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<tr>
<td>Low recurrence score (0–10)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No chemotherapy</td>
<td>High</td>
<td>281</td>
<td>27.2±4.5</td>
<td>2.09 (1.47–2.96)</td>
<td>7.4±3.4</td>
<td>2.20 (0.95–5.08)</td>
</tr>
<tr>
<td>No chemotherapy</td>
<td>Low</td>
<td>879</td>
<td>13.3±1.5</td>
<td>2.6±0.8</td>
<td></td>
<td></td>
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<tr>
<td>Intermediate recurrence score (11–25)</td>
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<td></td>
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</tr>
<tr>
<td>No chemotherapy</td>
<td>High</td>
<td>577</td>
<td>23.2±2.6</td>
<td>1.56 (1.21–2.00)</td>
<td>9.3±1.9</td>
<td>2.61 (1.65–4.11)</td>
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<td>No chemotherapy</td>
<td>Low</td>
<td>1605</td>
<td>13.6±1.1</td>
<td>3.5±0.6</td>
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<td>Chemotherapy</td>
<td>High</td>
<td>603</td>
<td>22.6±2.3</td>
<td>1.61 (1.27–2.04)</td>
<td>8.3±1.5</td>
<td>2.49 (1.60–3.87)</td>
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<td>Chemotherapy</td>
<td>Low</td>
<td>1568</td>
<td>15.7±1.3</td>
<td>4.0±0.7</td>
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<tr>
<td>High recurrence score (26–100)</td>
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<tr>
<td>Chemotherapy</td>
<td>High</td>
<td>542</td>
<td>32.1±4.4</td>
<td>1.85 (1.28–2.66)</td>
<td>19.8±3.9</td>
<td>3.35 (1.82–6.14)</td>
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<td>Chemotherapy</td>
<td>Low</td>
<td>414</td>
<td>19.3±3.8</td>
<td>7.0±2.4</td>
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<td><strong>Patients ≤50 yr</strong></td>
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<tr>
<td>Low recurrence score (0–10)</td>
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</tr>
<tr>
<td>No chemotherapy</td>
<td>High</td>
<td>64</td>
<td>9.3±4.5</td>
<td>0.68 (0.24–1.92)</td>
<td>0</td>
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<td>No chemotherapy</td>
<td>Low</td>
<td>348</td>
<td>13.3±2.3</td>
<td>1.8±0.9</td>
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<td>Intermediate recurrence score (11–25)</td>
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<td></td>
</tr>
<tr>
<td>No chemotherapy</td>
<td>High</td>
<td>265</td>
<td>19.8±3.0</td>
<td>1.27 (0.89–1.83)</td>
<td>12.3±2.4</td>
<td>3.06 (1.78–5.25)</td>
</tr>
<tr>
<td>No chemotherapy</td>
<td>Low</td>
<td>835</td>
<td>17.4±1.8</td>
<td>4.7±1.0</td>
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<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>High</td>
<td>252</td>
<td>13.5±3.0</td>
<td>1.19 (0.76–1.88)</td>
<td>6.1±1.8</td>
<td>2.20 (1.10–4.40)</td>
</tr>
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<td>Chemotherapy</td>
<td>Low</td>
<td>791</td>
<td>11.3±1.4</td>
<td>3.9±1.0</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>High</td>
<td>228</td>
<td>24.0±4.2</td>
<td>2.27 (1.22–4.19)</td>
<td>15.2±3.3</td>
<td>2.87 (1.23–6.65)</td>
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<tr>
<td>Chemotherapy</td>
<td>Low</td>
<td>175</td>
<td>14.8±4.2</td>
<td>6.2±2.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Plus–minus values are Kaplan–Meier estimates ±SE.† A hazard ratio greater than 1 indicates that high clinical risk was prognostic for a higher event rate. Confidence intervals have not been adjusted, and inferences drawn from the intervals may not be reproducible.

**Estimation of Chemotherapy Benefit in Reducing Distant Recurrence at 9 Years**

We previously reported that the estimated absolute reduction in the mean (±SE) rate of distant recurrence at 9 years associated with adjuvant chemotherapy among women 50 years of age or younger was 1.6±1.9 percentage points in those with a recurrence score of 16 to 20 and 6.4±4.9 percentage points in those with a recurrence score of 26 to 100. This suggests that chemotherapy may be particularly beneficial for women with high clinical risk.
score of 21 to 25. Here, we provide estimates of the absolute benefit of chemotherapy, further stratified according to clinical risk (Table 2). In 476 women with a recurrence score of 21 to 25, the absolute chemotherapy benefit in the subgroup with low clinical risk (6.4±4.9 percentage points) was similar to that in the subgroup with high clinical risk (8.7±6.2 percentage points). In the 886 women with a recurrence score of 16 to 20, there was an estimated chemotherapy benefit with high clinical risk (6.5±4.9%) but not with low clinical risk (−0.2±2.1%). The sample size was small in some of the subgroups examined; this contributed to higher standard errors than estimates for the entire cohort with a recurrence score of 11 to 25.

**PROGNOSIS IN WOMEN 50 YEARS OF AGE OR YOUNGER**

Among women who were 50 years of age or younger, most of whom were premenopausal and treated with tamoxifen alone or followed sequentially with an aromatase inhibitor, the distant recurrence rate at 9 years was less than 5% (≤1.8±0.9%) among those with a low recurrence score, irrespective of clinical risk, and an intermediate recurrence score with low clinical risk (4.7±1.0%) (Table 1). In contrast, the rate of distant recurrence at 9 years exceeded 10% among women with high clinical risk and an intermediate recurrence score who received endocrine therapy alone (12.3±2.4%) and in those with a high recurrence score who received chemoendocrine therapy (15.2±3.3%).

**DISCUSSION**

The recurrence score based on the 21-gene breast cancer assay provides robust prognostic information regarding distant recurrence and predicts chemotherapy benefit or lack thereof; clinicopathological features provide prognostic information that is complementary to that of this assay. The integration of genomic and clinical information may provide a more accurate estimation of prognosis for individual patients than could be provided by either the genomic or clinical information alone. Our analysis confirmed that clinical-risk stratification based on tumor size and histologic grade, when added to the 21-gene recurrence score, provided prognostic information about recurrence but not predictive information regarding chemotherapy benefit.

Although TAILORx showed that endocrine therapy was noninferior to chemoendocrine therapy in women with an intermediate recurrence score (a score of 11 to 25), we performed an exploratory analysis in accordance with recommended guidelines in order to determine whether any subgroup might derive some benefit from adjuvant chemotherapy. There was a significant interaction between chemotherapy treatment, age (≤50 vs. >50 years) or menopausal status, and recurrence score, suggesting a modest but clinically meaningful reduction in the rate of distant recurrence with chemotherapy among younger or premenopausal women who had a recurrence score of 16 to 25. Similar findings were noted in a population-based study indicating a chemotherapy benefit emerging at a recurrence score above 15 in women who were 50 years of age or younger and above 25 in women who were older than 50 years.

Adjuvant chemotherapy is associated with nearly twice the reduction in the rate of death from breast cancer among women younger than 50 years of age as compared with older women; this has been attributed to a dual effect, which includes a direct cytotoxic effect in eradicating micrometastatic disease and an antiestrogenic effect from chemotherapy-induced ovarian failure and premature menopause. The interaction among age, recurrence score, and chemotherapy benefit observed in TAILORx is therefore consistent with the greater treatment effect of adjuvant chemotherapy in younger women.

Although the potential pitfalls of a subgroup analysis to identify more effective therapies in trials with a superiority design have been well described and the exploratory analyses presented here were not adjusted for multiple comparisons, caution is warranted when withdrawing potentially lifesaving therapy on the basis of a noninferiority trial such as TAILORx, especially when the findings are biologically plausible and supported by population-level data, as described here. Given the incremental benefits observed with ovarian suppression plus tamoxifen or an aromatase inhibitor as compared with tamoxifen alone in premenopausal women and the low percentage of premenopausal women who received ovarian suppression in TAILORx, it is possible that similar incremental benefits
observed in younger women who received chemotherapy and had a recurrence score of 16 to 25 could be achieved with ovarian suppression and an aromatase inhibitor, as observed in other trials.\(^{21,22}\) This potential is supported by data indicating that a low-to-midrange recurrence score and high estrogen receptor 1 gene (ESR1) RNA expression are predictive of benefit from tamoxifen.\(^{23,24}\) For patients who are approaching menopause, a strategy of an initial 2-to-5-year course of tamoxifen followed by a switch to an aromatase inhibitor at the time of natural menopause is another reasonable approach.\(^{25}\) This may be especially true for women with a high ESR1 RNA score obtained as part of the 21-gene assay, which is prognostic for late recurrence 5 or more years after diagnosis and thus may identify women who are more likely to benefit from continued antiestrogen therapy beyond 5 years.\(^{26}\)

Recurrence rates reflect the underlying recurrence risk, the benefit from adjuvant endocrine therapy, and the benefit from adjuvant chemotherapy, the latter of which has little effect on nonrecurrence events such as contralateral breast cancer or second primary cancers.\(^{27-29}\) Estimation of an absolute chemotherapy benefit requires tools to estimate the underlying risk of recurrence and the treatment effect of chemotherapy, which may vary in magnitude according to tumor biologic features.

When the recurrence score was further stratified according to clinical risk among TAILORx patients as described here, there was no evidence of chemotherapy benefit at 9 years, according to use or nonuse of adjuvant chemotherapy in women younger than 50 years of age.\(^{30}\) The New England Journal of Medicine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Recurrence score of 16–20</th>
<th>Recurrence score of 21–25</th>
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<td></td>
<td>Estimated Probability of Recurrence, Second Primary Cancer, or Death (95% CI)†</td>
<td>Estimated Probability of Distant Recurrence (95% CI)†</td>
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<td>Hazard Ratio for Distant Recurrence (95% CI)†</td>
<td>Hazard Ratio for Distant Recurrence (95% CI)†</td>
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<tr>
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<td>No. of Patients</td>
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<td>72</td>
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</table>

* Plus-minus values are Kaplan–Meier estimates ±SE. An estimated hazard ratio of greater than 1 indicates a higher recurrence rate with endocrine therapy alone than with chemoendocrine therapy. Confidence intervals have not been ad-
cal risk also added prognostic information for women with a high recurrence score who were receiving chemoendocrine therapy, irrespective of age, and thus could be used to identify patients with very high risk for whom testing of new therapeutic approaches in clinical trials is warranted.

In conclusion, binary clinical-risk stratification based on tumor size and histologic grade added prognostic information to the 21-gene recurrence score, but not prediction of a large chemotherapy benefit. The addition of this information enabled more precise identification of subgroups of younger women who may derive some benefit from more effective antiestrogen therapy than a course of tamoxifen.

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. government.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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