The impact of the 21-gene Recurrence Score assay on clinical decision-making in node-positive (up to 3 positive nodes) estrogen receptor-positive breast cancer patients

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Abstract Oncotype DX testing is reimbursed in Israel for node-negative and node-positive (N1+; up to 3 positive nodes including micrometastases), estrogen receptor positive (ER+), breast cancer patients. This retrospective study evaluated the impact of Oncotype DX testing on treatment decisions in N1+/ER+ breast cancer patients. To this end, we compared treatments for all N+ patients for whom testing had been ordered with treatments for patients with similar characteristics where the test had not been available. The retrospective analysis included 951 patients (282 Oncotype DX, 669 controls), all of whom received endocrine therapy with or without chemotherapy. In Oncotype DX patients, 7.1, 37.0, and 100 % of those with low, intermediate, and high Recurrence Score results (Onco
type DX summary score) received chemotherapy, respectively ($P < 0.0001$, all comparisons). Chemotherapy use was lower in Oncotype DX patients versus controls (24.5 vs. 70.1 %). In a multivariate logistic regression analysis in which the probability of receiving chemotherapy was modeled as a function of Oncotype DX testing, age, tumor size, tumor grade, nodal status, and the interactions between Oncotype DX testing and the other covariates, Oncotype DX testing was associated with significantly lower odds of receiving chemotherapy (odds ratio 0.16; 95 % CI 0.11–0.24; $P < 0.0001$). In summary, our findings suggest that Oncotype DX testing has a significant impact on reducing chemotherapy use in N1+/ER+ breast cancer patients in Israel.

Keywords Adjuvant chemotherapy · Breast cancer · Decision-making · Node positive · Oncotype DX · Recurrence Score

Introduction

The St. Gallen Consensus Conference 2011 reflected a transition to the predominance of tumor biology rather than anatomical disease indicators (e.g., tumor size, extent of nodal involvement) for clinical decision-making in breast cancer (BC) [1]. Notably, the majority of the panelists at the St. Gallen Consensus Conference did not consider nodal involvement (up to 3 positive axillary lymph nodes) as a sufficient reason for giving adjuvant chemotherapy, whereas they did consider high grade (grade 3), human epidermal growth factor receptor 2
(HER2) overexpression, and having a “triple negative” disease [i.e., lack of expression of the estrogen receptor (ER), progesterone receptor (PR), and HER2] as sufficient reasons for such a treatment [1]. The panel at the conference agreed that the summary risk score (Recurrence Score®, a numeric score between 0 and 100) derived from the 21-gene reverse transcriptase-polymerase chain reaction Oncotype DX® assay (Genomic Health, Inc., Redwood City, CA) may be useful for making adjuvant treatment decisions for ER+ patients in whom uncertainty remains after considering other factors (e.g., grade, HER2 status, etc.) [1]. The Recurrence Score as a predictor of likely benefit of chemotherapy has also been acknowledged by the American Society of Clinical Oncology [2], the National Comprehensive Cancer Network [3], and the European Society for Medical Oncology [4].

The Oncotype DX assay was validated (level I, category B evidence [5]) to quantify the risk of distant recurrence in tamoxifen-treated node-negative ER+ BC patients and to predict the benefit of chemotherapy in these patients [6–9]. Subsequently, the Recurrence Score has been demonstrated to also be a prognosticator as well as a predictor of the benefit of chemotherapy in node-positive (N+) ER+ BC patients treated with endocrine therapy [10–13]. The ongoing randomized phase 3 SWOG S1007 trial will determine the effect of chemotherapy plus endocrine therapy versus endocrine therapy alone in N+ hormone receptor positive BC patients with Recurrence Score ≤25 and will therefore provide insights into the interaction between treatment received, clinical outcome, and the continuous Recurrence Score value for patients within this score interval [14].

In Israel, the Oncotype DX assay is widely used and is reimbursed by all health-care organizations. Clalit Health Services (CHS), Israel’s largest health-care organization with 3.6 million members, approved Oncotype DX reimbursement for node-negative ER+ BC patients in February 2006 and extended its reimbursement policy in January 2008 to include reimbursement for both node-negative and N1+ (up to 3 positive axillary lymph nodes including micrometastases) ER+ BC patients.

The impact of the Oncotype DX assay on clinical practice has been evaluated in several studies in node-negative ER+ BC patients [15–27]; however data on the impact of the Oncotype DX assay on treatment recommendations in N+ ER+ BC patients are limited [25–29]. The current study was designed to evaluate the impact of the Recurrence Score results on treatment decisions in N1+ ER+ HER2 negative BC patients and to compare treatment decisions in this patient group with those in a control group comprised of patients in whom treatment decisions were made based on clinicopathologic parameters alone.

Materials and methods

Study design

The study was approved by the institutional review boards of the participating institutions.

This retrospective study compared treatment decisions in 2 patient groups. The first group (“Oncotype DX”) included all patients with N1+, ER+, HER2 negative, BC patients who were diagnosed and had the Oncotype DX assay between 2006 and 2009 through CHS. The second group (controls) was identified by reviewing all patients treated in the participating medical centers and including patients (diagnosed between 2000 and 2010) for whom treatment decisions were based on clinicopathologic parameters alone and whose baseline characteristics were similar to those in the “Oncotype DX” group.

Data source

For the Oncotype DX group, researchers collected information from patients’ files on relevant biological data and the treatments received. For the control group, relevant information was collected from the medical records of relevant patients treated in 4 medical centers in Israel (Institute of Oncology-Davidoff Center, Kaplan Medical Center, Lin Medical Center, and Soroka University Medical Center).

Statistical analysis

Descriptive statistics were used to summarize patient and tumor characteristics and treatment received. Fisher’s exact test was used in pairwise comparisons of chemotherapy treatment percentages among the Recurrence Score groups. Logistic regression analyses were used to compare the probability of treatment between the Oncotype DX group and the control group (including age group, tumor size, tumor grade, and nodal status as covariates).

Results

A total of 951 patients were included in the analysis (282 Oncotype DX, 669 controls; Table 1). The vast majority of the Oncotype DX patients (272 patients, 96.4 %) were diagnosed from 2008 onward, whereas the vast majority of the controls (588 patients, 87.9 %) were diagnosed prior to 2008. The groups were unbalanced with respect to tumor size, tumor grade, and nodal status, with the clinical and pathological characteristics of the control group associated with more chemotherapy use compared with those of the Oncotype DX group (i.e., larger tumors, higher proportion
of patients with grade 3 tumors, and higher proportions of patients with 1, 2, and 3 positive nodes; Table 1).

Recurrence Score outcomes and clinicopathologic characteristics

In the Oncotype DX group, the mean Recurrence Score (SD) result was 18.2 (9.2) with a range of 0–58. Of the 282 patients in the Oncotype DX group, 156 patients (55.3 %) had a low Recurrence Score result (<18), 108 patients (38.3 %) had an intermediate Recurrence Score result (18–30), and 18 patients (6.4 %) had a high Recurrence Score result (>31) (Table 2). The distributions of age, tumor size, tumor grade, and nodal status in the 3 categories are shown in Table 2. The Recurrence Score result was significantly associated with tumor grade, with higher Recurrence Score results associated with higher histologic grade (Spearman correlation; \( P = 0.0001 \)) and there was a trend toward significance with tumor size (higher

| Table 1 Baseline patient and tumor characteristics |
|---------------------------------------------------|
| **Onco** DX group | **Controls** |
| **N = 282** | **N = 669** |
| **Age** | | |
| Median (range), years | 61.5 (36–87) | 59.0 (24–93) |
| Age category\(^a\), N (%) | | |
| <40 years | 6 (2.1) | 34 (5.1) |
| 40–55 years | 88 (31.2) | 224 (33.5) |
| >55 years | 188 (66.7) | 411 (61.4) |
| **Tumor size\(^b\)** | | |
| Mean (SD)\(^c\), cm | 1.87 (1.0) | 2.1 (1.0) |
| Median (range), cm | 1.6 (up to 6.5) | 1.9 (up to 6) |
| **Tumor grade category\(^d\,e\), N (%)** | | |
| Grade 1 | 40 (14.2) | 75 (11.2) |
| Grade 2 | 155 (55.0) | 323 (48.0) |
| Grade 3 | 46 (16.3) | 194 (29.0) |
| Not applicable/unknown | 41 (14.5) | 77 (11.5) |
| **Nodal involvement\(^f\), N (%)** | | |
| Micrometastases | 135 (47.9) | 82 (12.3) |
| 1 positive node | 101 (35.8) | 338 (50.5) |
| 2 positive nodes | 38 (13.5) | 160 (23.9) |
| 3 positive nodes | 8 (2.8) | 89 (13.3) |

**SD** standard deviation

\(^a\) \( P = 0.069 \) (comparing age distribution; \( \chi^2 \) test)

\(^b\) In cases of multicentric or bilateral disease, the largest tumor and the highest grade were considered for the analysis; tumor size information was not available for 3 patients in the intermediate Recurrence Score group

\(^c\) \( P = 0.0005 \) (Mann–Whitney test)

\(^d\) \( P = 0.0001 \) (comparing tumor grade distribution; \( \chi^2 \) test)

\(^e\) \( P < 0.0001 \) (comparing nodal status distribution; \( \chi^2 \) test)

Recurrence Score outcomes and treatments received: subanalysis by tumor size, grade, and nodal status

Treatments received were also analyzed by subgroups including age (<55 and >55 years of age), tumor size (<1, 1–2, and >2 cm), tumor grade (1–3), and nodal status (micrometastases and 1, 2, and 3 positive nodes). In all subgroups analyzed, all high Recurrence Score patients received chemotherapy, and a higher proportion of intermediate Recurrence Score patients received chemotherapy compared with low Recurrence Score patients (Fig. 1). Furthermore, in all subgroups analyzed, the overall proportion of Oncotype DX patients receiving chemotherapy was lower compared with controls (Fig. 1). However, since the Oncotype DX and the control groups were unbalanced with respect to baseline characteristics associated with chemotherapy use (i.e., tumor size, tumor grade, and nodal involvement; Table 1), we performed a multivariate logistic regression analysis (adjusting for these variables) to assess the statistical significance of the observed difference in chemotherapy use between these 2 patient groups.

Chemotherapy use in the Oncotype DX and control groups: multivariate logistic regression analyses

We modeled the probability of receiving adjuvant chemotherapy (using multivariate logistic regression on the entire cohort) as a function of having Oncotype DX testing
(yes/no), age group (<40, 40–55, and >55 years), tumor size (<1, 1–2, and, >2 cm), tumor grade (grade 1–3), number of positive nodes (micrometastases, and 1, 2, and 3 positive nodes), as well as the interactions between testing and each of the other covariates (these interactions were found to be non-significant). Patients with missing data on any covariate were excluded. Patients who underwent Oncotype DX testing had significantly lower odds of receiving chemotherapy compared with control patients who were not tested (OR 0.16; \( P < 0.0001 \)), as were patients >55 years of age (vs. patients <40 and 40–55 years of age), patients with grade 1 tumors (vs. patients with grades 2 and 3 tumors), and patients with micrometastases (vs. patients with 1, 2, and 3 positive nodes) (Table 4). The odds of receiving chemotherapy were similar for patients with 1 and 2 positive nodes; however, patients with 3 positive nodes had significantly increased odds of receiving chemotherapy compared with those with either 1 or 2 positive nodes (\( P < 0.005 \)) (Table 4).

### Table 2: Distribution of age, tumor size, tumor grade, and nodal status by Recurrence Score categories in the Oncotype DX group

| Recurrence Score | Low (<18) | Intermediate (18–30) | High (≥31) |
|------------------|-----------|----------------------|------------|
| \( n \)          | 156       | 108                  | 18         |
| Age              |           |                      |            |
| Median (range), year | 62 (39–87) | 60 (36–78)          | 62.5 (38–73) |
| Age category, \( n \) |           |                      |            |
| <40 (\( n = 6 \)) | 2         | 2                    | 2          |
| 40–55 (\( n = 88 \)) | 49       | 34                   | 5          |
| >55 (\( n = 188 \)) | 105      | 72                   | 11         |
| Tumor size, \( \text{mean (SD), cm} \) | 1.7 (0.8) | 2.0 (1.2)          | 2.3 (1.2)  |
| Tumor grade category, \( n \) |           |                      |            |
| Grade 1 (\( n = 40 \)) | 34       | 6                    | 0          |
| Grade 2 (\( n = 155 \)) | 93       | 55                   | 7          |
| Grade 3 (\( n = 46 \)) | 12       | 26                   | 8          |
| Not applicable/unknown (\( n = 41 \)) | 17      | 21                   | 3          |
| Nodal involvement, \( n \) |           |                      |            |
| Micrometastases (\( n = 135 \)) | 78       | 44                   | 13         |
| 1 positive node (\( n = 101 \)) | 58       | 40                   | 3          |
| 2 positive nodes (\( n = 38 \)) | 17       | 20                   | 1          |
| 3 positive nodes (\( n = 8 \)) | 3        | 4                    | 1          |


### Table 3: Adjuvant treatment received by Recurrence Score category

| Treatment | Oncotype DX group | Controls | Recurrence Score |
|-----------|-------------------|----------|------------------|
|           | Low (<18) | Intermediate (18–30) | High (≥31) | All | All |
| \( n \) | 156 | 108 | 18 | \( N = 282 \) | \( N = 669 \) |
| % | No. | % | No. | % | No. | % | No. |%
| Chemotherapy plus endocrine therapy | 11 | 7.1 | 40 | 37.0 | 18 | 100.0 | 69 | 24.5 | 469 | 70.1 |
| Endocrine therapy | 145 | 92.9 | 68 | 63.0 | 0 | 0.0 | 213 | 75.5 | 200 | 29.9 |

\( a \) \( P < 0.0001 \) for comparing proportions of patients receiving chemotherapy between the low, intermediate, and high Recurrence Score groups (all comparisons)

\( b \) Adjusted odds ratio for receiving chemotherapy in Oncotype DX patients versus controls, 0.16; 95 % Wald confidence limits, 0.11–0.24; adjusted for age, tumor size, grade, and nodal status
Fig. 1 Proportions of patients receiving chemotherapy by Recurrence Score category and age group (a), tumor size (b), grade (c), and nodal status (d). Int intermediate, micromets micrometastases, y year. Only 6 patients were <40 years of age; tumor size information was not available for 3 patients in the intermediate Recurrence Score group; grade information was not applicable/not available for 41 patients in the Oncotype DX group and 77 controls. In cases of multicentric or bilateral disease, the largest tumor and the highest grade were considered for the analysis.
A second multivariate logistic regression analysis was performed for each of the age groups separately (Table 5). Since the group of patients <40 years of age included only 6 Oncotype DX patients, no reliable conclusions could be drawn. For the 2 remaining age groups (40–55 years of age and >55 years of age), the probability of receiving adjuvant chemotherapy was modeled as a function of tumor size (1, 1–2, and >2 cm), tumor grade (grade 1–3), number of positive nodes (micrometastases, 1, 2, or 3 positive nodes), and the interactions between testing and each of the other covariates (these interactions were found to be non-significant). In both age groups, Oncotype DX testing was associated with significantly lower odds of receiving chemotherapy, although the effect was more pronounced in patients aged 40–55 years compared with those aged >55 years (ORs 0.067 and 0.24, respectively; \( P < 0.0001 \) for both). In the younger patient group, tumor grade had a significant impact on the odds of receiving chemotherapy, whereas in the older patient group, both tumor grade and nodal status had a significant impact on the odds of receiving chemotherapy (Table 5).

**Discussion**

The current study suggests that Oncotype DX testing has a significant impact on oncologists’ decision to treat N1+ ER+ BC patients with chemotherapy. The use of Oncotype DX testing was associated with a reduction in the use of chemotherapy in this patient population by 65 %.

**Table 4** Odds ratios for receiving chemotherapy (logistic regression analysis on the entire cohort)

| Effect                        | Odds ratio | 95 % Wald confidence limits | \( P \) value |
|--------------------------------|------------|-----------------------------|--------------|
| Oncotype DX testing (vs. no testing) | 0.16       | 0.11–0.24                   | <0.0001      |
| Age                            |            |                             |              |
| 40–55 vs. <40 years            | 1.15       | 0.42–3.16                   | 0.78         |
| >55 vs. <40 years              | 0.27       | 0.10–0.72                   | 0.0088       |
| >55 vs. 40–55 years            | 0.24       | 0.16–0.34                   | <0.0001      |
| Tumor size                     |            |                             |              |
| 1–2 vs. <1 cm                  | 0.46       | 0.25–0.83                   | 0.0095       |
| >2 vs. <1 cm                   | 0.64       | 0.35–1.15                   | 0.14         |
| >2 vs. 1–2 cm                  | 1.40       | 0.98–1.98                   | 0.063        |
| Tumor grade                    |            |                             |              |
| Grade 2 vs. 1                  | 1.76       | 1.08–2.85                   | 0.023        |
| Grade 3 vs. 1                  | 3.88       | 2.21–6.79                   | <0.0001      |
| Grade 3 vs. 2                  | 2.21       | 1.47–3.30                   | 0.0001       |
| Nodal status                   |            |                             |              |
| 1 positive node vs. micrometastases | 1.66     | 1.05–2.63                   | 0.029        |
| 2 positive nodes vs. micrometastases | 1.91     | 1.12–3.24                   | 0.017        |
| 3 positive nodes vs. micrometastases | 7.29     | 3.36–15.84                  | <0.0001      |
| 2 vs. 1 positive nodes         | 1.15       | 0.76–1.75                   | 0.52         |
| 3 vs. 1 positive nodes         | 4.38       | 2.17–8.86                   | <0.0001      |
| 3 vs. 2 positive nodes         | 3.82       | 1.81–8.08                   | 0.0004       |

A total of 118 patients were excluded from the analysis due to missing data

* Interactions between Oncotype DX testing and each of the other covariates were found to be non-significant

Bold values represents statistically significant odds ratios
All patients with high Recurrence Score results were treated with chemotherapy, whereas those with low Recurrence Score results rarely received chemotherapy.

Our findings, based on recent treatment patterns in N1+ ER+ BC patients in Israel, are consistent with findings from studies in node-negative populations around the world. These studies demonstrated that in 19–44 % of evaluated cases, recommendations for adjuvant treatment were changed after receiving the Recurrence Score results [15–27]. Of the patients for whom treatment recommendations were changed, the most frequent change was from chemotherapy plus endocrine therapy to endocrine therapy alone (52–89 % of cases); however, a clinically relevant proportion of patients were identified as likely to derive a significant benefit from the addition of chemotherapy [15–18, 20, 21, 23–26].

The current study is also consistent with the limited available data on the impact of the Recurrence Score results on treatment recommendations in the N0 ER+ BC patient population [25–29]. For example, in a recent analysis, in which treatment recommendations pre- and post-knowledge of Recurrence Score results were analyzed for a mixed patient population of whom only 15 % were N+, knowing the Recurrence Score results led to a 25 % overall change in treatment recommendations (up to 89 % of these changes were from chemotherapy plus endocrine therapy to endocrine therapy alone) [28]. Furthermore, in a recent physician survey, in which 160 medical oncologists in the United States provided information on their most recent N+ ER+ BC patient, 51 % of the medical oncologists changed their treatment recommendations after obtaining the Recurrence Score result, with the most frequent change (65 % of cases) being from chemotherapy plus endocrine therapy to endocrine therapy alone [29]. Our study is also consistent with a recent prospective study in Germany that showed a treatment recommendation change in 38.5 % of 122 evaluated N+ ER+ BC patients, with the most frequent change (72 % of cases) being from chemotherapy plus endocrine therapy to endocrine therapy alone [27].

Interestingly, our logistic regression analysis showed that the impact of Oncotype DX testing on reducing the odds of receiving chemotherapy was more pronounced in patients aged 40–55 years, than in patients ≥55 years of age, suggesting that in older patients, in whom chemotherapy treatment was less common overall, Oncotype DX testing had a lower impact on changing treatment decisions. These findings provide insight into the decision-making process in the molecular profiling era by highlighting the patient populations for whom oncologists tend to recommend chemotherapy before knowing the Recurrence Score results (due to high baseline risk for recurrence in younger patients overall), but given the opportunity to individualize treatment decisions, are likely to treat

### Table 5 Odds ratios for receiving chemotherapy (logistic regression analysis on each age group)

| Effect                       | Odds ratio (95% Wald confidence limits) | Patients aged 40–55 years | Odds ratio (95% Wald confidence limits) | Patients aged ≥55 years |
|------------------------------|----------------------------------------|---------------------------|----------------------------------------|-------------------------|
| Oncotype DX testing (vs. no testing) | 0.067 (0.03–0.15) | <0.0001 | 0.24 (0.15–0.39) | <0.0001 |
| Tumor size                   |                                        |                           |                                        |                         |
| 1–2 vs. <1 cm                | 0.26 (0.068–0.97) | 0.046 | 0.56 (0.28–1.12) | 0.10 |
| >2 vs. <1 cm                 | 0.52 (0.14–1.94) | 0.33 | 0.73 (0.36–1.46) | 0.37 |
| >2 vs. 1–2 cm                | 2.03 (0.98–4.21) | 0.056 | 1.29 (0.85–1.97) | 0.23 |
| Tumor grade                  |                                        |                           |                                        |                         |
| Grade 2 vs. 1                | 2.40 (0.94–6.12) | 0.067 | 1.50 (0.84–2.67) | 0.17 |
| Grade 3 vs. 1                | 5.08 (1.58–16.27) | 0.0063 | 3.01 (1.56–5.81) | 0.001 |
| Grade 3 vs. 2                | 2.12 (0.84–5.32) | 0.11 | 2.02 (1.27–3.21) | 0.0031 |
| Nodal status                 |                                        |                           |                                        |                         |
| 1 positive node vs. micrometastases | 1.66 (0.69–3.96) | 0.26 | 1.75 (0.99–3.11) | 0.055 |
| 2 positive nodes vs. micrometastases | 1.33 (0.44–4.04) | 0.61 | 2.18 (1.15–4.15) | 0.017 |
| 3 positive nodes vs. micrometastases | 4.19 (0.70–24.88) | 0.12 | 8.15 (3.38–19.67) | <0.0001 |
| 2 vs. 1 positive nodes       | 0.80 (0.31–2.07) | 0.65 | 1.24 (0.77–2.00) | 0.37 |
| 3 vs. 1 positive nodes       | 2.53 (0.46–13.99) | 0.29 | 4.65 (2.16–10.01) | <0.0001 |
| 3 vs. 2 positive nodes       | 3.14 (0.51–19.56) | 0.22 | 3.74 (1.65–8.45) | 0.0015 |

For the patients aged 40–55, 31 out of 312 patients were excluded from the analysis due to missing data; for the patients aged ≥55 years, 84 out of 599 patients were excluded from the analysis due to missing data

*a* Interactions between Oncotype DX testing and each of the other covariates were found to be non-significant

Bold values represent statistically significant odds ratios
patients with endocrine therapy alone if the Recurrence Score result is low. Notably, these treatment patterns are consistent with the recent St. Gallen consensus document stating that chemotherapy is not necessarily mandated in patients with ER+, HER2 negative disease with 1–3 positive nodes [1].

From a patient’s perspective, Oncotype DX testing may prevent unnecessary chemotherapy and its associated toxicity, thereby affecting quality of life. Furthermore, 3 studies have recently demonstrated that patients report significantly lower conflict about their treatment decision and decreased situational anxiety after receiving their Recurrence Score result [15, 27, 30].

Reducing the proportion of patients receiving chemotherapy has economic implications. In the ER+ node-negative BC population in Israel, Klang et al. [18] have shown that Oncotype DX testing leads to reduced chemotherapy use, and estimated that Oncotype DX testing is associated with a net gain of 0.170 quality-adjusted life years (QALY) per patient (due to reducing disutility associated with chemotherapy and cancer recurrence) and that the cost-effectiveness ratio is $10,770 per QALY gained. There have been very few studies assessing the cost-effectiveness of Oncotype DX in the N+ ER+ BC population. The only study published to date is a UK-based analysis which showed that using Oncotype DX is likely to be cost-effective versus current clinical practice in this patient population [31]. As the current study shows significant reductions in chemotherapy use in the ER+ N1+ BC population, findings from a health economic analysis may be consistent with those from the UK study [31]. A formal assessment of the cost-effectiveness of using Oncotype DX in the Israeli ER+ N+ BC population is warranted and is currently being planned.

This study has several limitations. Most notably, the 2 patient groups were unbalanced with respect to baseline characteristics. Patients in the Oncotype DX group had, on average, smaller tumors, and the group had lower frequencies of patients with grade 3 tumors and those with 1, 2, and 3 positive nodes compared with controls. These differences probably stem from the discrepancy in the period of diagnosis (most of the Oncotype DX patients were diagnosed from 2008 onward, whereas most of the controls were diagnosed prior to 2008), and may therefore reflect earlier BC diagnosis in the Oncotype DX patients due to advances in BC awareness and screening over time. Since all of these characteristics impact chemotherapy use (Oncotype DX patients had characteristics associated with less chemotherapy use), we performed a multivariate logistic regression analysis (adjusting for age, tumor size, tumor grade, and nodal status) to assess the statistical significance of the observed reduction in chemotherapy use with Oncotype DX testing, and demonstrated that testing was significantly associated with reduced odds of receiving chemotherapy (after adjustment for these known imbalances). Although such an analysis is unlikely to capture all imbalances between the groups (i.e., factors not measured/included in the logistic regression model such as PR status), the calculated ORs strongly suggest that the observed reduction in chemotherapy use in the Oncotype DX group was statistically significant. Another limitation of this study stemming from the aforementioned difference in the period of diagnosis between the 2 groups is the potential shift in adjuvant treatment recommendations for this patient population over time. In addition, there may have been selection bias in the small proportion of control patients who were diagnosed after 2008 (i.e., after Oncotype DX was available in Israel for N+ patients), as these could represent a subgroup of patients for whom oncologists felt that the clinicopathologic characteristics were enough to recommend treatment without ordering Oncotype DX testing. Notably, the logistic regression analysis would have addressed this limitation to a large extent. Finally, the sample size of some of the subgroups in the Oncotype DX group (specifically, patients <40 years of age) was relatively small and therefore no conclusions could be drawn regarding these subgroups.

In summary, our study demonstrates that since becoming available for N1+ ER+ BC patients in Israel in 2008, Oncotype DX testing has caused a dramatic shift in the treatment paradigm for this patient population. The economic impact of this paradigm shift has yet to be evaluated.

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Conflict of interest L. Soussan-Gutman reports being employed by and holding stock options in Teva Pharmaceutical Industries Ltd. and serving as a consultant for Genomic Health Inc. C. Svedman reports being employed by and holding stock options in Genomic Health, Inc. N. Ben Baruch reports having received an honorarium from Genomic Health Inc. S.M. Stemmer, S.H. Klang, D.B. Gefen, M. Steiner, S. Merling, S. Rizel, and N. Lieberman declare no conflict of interest.

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References

1. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thurlimann B, Senn HJ (2011) Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the primary therapy of early breast cancer 2011. Ann Oncol 22(8):1736–1747. doi:10.1093/annonc/mdr304

2. Harris L, Fritsche H, Mennel R, Norton L, Ravdin P, Taube S, Somerfield MR, Hayes DF, Bast RC Jr (2007) American Society
of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol 25(33):5287–5312. doi:10.1200/JCO.2007.14.2364
3. NCCN (2012) NCCN clinical practice guidelines in oncology. Version 3.2012. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed 31 Dec 2012
4. Aebi S, Davidson T, Gruber G, Cardoso F, Group EGW (2011) Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 22(Suppl 6):viii2–vii24. doi:10.1093/annonc/mdr371
5. Simon RM, Paik S, Hayes DF (2009) Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst 101(21):1446–1452. doi:10.1093/jnci/djp335
6. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, Baehner FL, Walker MG, Watson D, Park T, Hiller W, Fisher ER, Wickerham DL, Bryant J, Wolmark N (2004) A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 351(27):2817–2826. doi:10.1056/NEJMoa041588
7. Habel LA, Shak S, Jacobs MK, Capra A, Alexander C, Pho M, Baker J, Walker M, Watson D, Hackett J, Blick NT, Greenberg D, Fehrenbacher L, Langholz B, Quesenberry CP (2006) A population-based study of tumor gene expression and risk of breast cancer death among lymph node-negative patients. Breast Cancer Res 8(3):R25. doi:10.1186/bcr1412
8. Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, Cronin M, Baehner FL, Watson D, Bryant J, Costantino JP, Geyer CE, Jr, Wickerham DL, Wolmark N (2006) Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 24(23):3726–3734. doi:10.1200/JCO.2005.04.7985
9. Toi M, Iwata H, Yamanaka T, Masuda N, Ohno S, Nakamura S, Nakayama T, Kashiwaba M, Kamigaki S, Kuroi K (2010) Clinical significance of the 21-gene signature (Oncotype DX) in hormone receptor-positive early stage primary breast cancer in the Japanese population. Cancer 116(13):3112–3118. doi:10.1002/cncr.25206
10. Goldstein LJ, Gray R, Badve S, Childs BH, Yoshizawa C, Rowley S, Shak S, Baehner FL, Radvan PM, Davidson NE, Sleege GW Jr, Perez EA, Shulman LN, Martino S, Sparano JA (2008) Prognostic utility of the 21-gene assay in hormone receptor-positive operable breast cancer compared with classical clinicopathologic features. J Clin Oncol 26(25):4063–4071. doi:10.1200/JCO.2007.14.4501
11. Albain KS, Barlow WE, Shak S, Hortobagyi GN, Livingston RB, Yeh IT, Radvan P, Bugarijn R, Baehner FL, Davidson NE, Sleege GW, Winer EP, Hudis C, Ingle JN, Perez EA, Pritchard KL, Shepherd L, Gralow JR, Yoshizawa C, Allred DC, Osborne CK, Hayes DF (2010) Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol 11(1):55–65. doi:10.1016/S1470-2045(09)70314-6
12. Dowsett M, Cuzick J, Wale C, Forbes J, Mallon EA, Salter J, Quinn E, Dunbier A, Shukla-Davey S, Howell A, Bugarijn R, Baehner FL, Shak S (2010) Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a translational study. J Clin Oncol 28(11):1829–1834. doi:10.1200/JCO.2009.24.4798
13. Mamounas EP, Tang G, Paik S, Baehner FL, Liu Q, Jeong J-H, Kim S-R, Butler SM, Jamshidian F, Cherubavaz DB, Sing AP, Shak S, Julian TB, Wickerham DL, Costantino JP, Wolmark N (2012) Association between the 21-Gene Recurrence Score (RS) and benefit from adjuvant paclitaxel (Pac) in node-positive (N+), ER-positive breast cancer patients (pts): Results from NSABP B-28. Paper presented at the San Antonio Breast Cancer Symposium (SABCS), San Antonio, TX, 4–8 December, 2012
14. ClinicalTrials.gov website. Description of the SWOG S1007 trial. (2011). http://www.clinicaltrials.gov/ct2/show/NCT01272037?term=swog-s-1007&rank=1. Accessed 24 Jan 2012
15. Lo SS, Mumbry PB, Norton J, Rychlik K, Smerage J, Kash J, Chew HK, Gaynor ER, Hayes DF, Epstein A, Albain KS (2010) Prospective multicenter study of the impact of the 21-gene recurrence score assay on medical oncologist and patient adjuvant breast cancer treatment selection. J Clin Oncol 28(10):1671–1676. doi:10.1200/JCO.2008.20.2119
16. Geffen DB, Abu-Ghannam S, Sion-Vardy N, Braunstein R, Tokar M, Ariad S, Delgado B, Bayme M, Koretz M (2011) The impact of the 21-gene recurrence score assay on decision making about adjuvant chemotherapy in early-stage estrogen-receptor-positive breast cancer in an oncology practice with a unified treatment policy. Ann Oncol 22(11):2381–2386. doi:10.1093/annonc/mdq769
17. Albanell J, Gonzalez A, Ruiz-Borrego M, Alba E, Garcia-Saenz JA, Corominas JM, Burgues O, Furio V, Rojo A, Palacios J, Bermejo B, Martinez-Garcia M, Limon ML, Munoz AS, Martin M, Tusquets I, Rojo F, Colomer R, Faull I, Lluch A (2012) Prospective transGISCAM study of the impact of the 21-gene Recurrence Score assay and traditional clinicopathological factors on adjuvant clinical decision making in women with estrogen receptor-positive (ER+) node-negative breast cancer. Ann Oncol 23:625–631. doi:10.1093/annonc/mdr278
18. Klang SH, Hammerman A, Liebermann N, Efraf N, Dobarne J, Hornberger J (2010) Economic implications of 21-gene breast cancer risk assay from the perspective of an Israeli-managed health-care organization. Value Health 13(4):381–387. doi:10.1111/j.1524-4733.2010.00489.x
19. Ademuyiwa FO, Miller A, O’Connor T, Edge SB, Thorat MA, Sleege GW, Levine E, Badve S (2011) The effects of Oncotype DX recurrence scores on chemotherapy utilization in a multi-institutional breast cancer cohort. Breast Cancer Res Treat 126(3):797–802. doi:10.1007/s10549-010-1329-6
20. Kamal AH, Loprinzi CL, Reynolds C, Dueck AC, Geiger XJ, Ingle JN, Carlson RW, Hobday TJ, Winer EP, Goetz MP (2011) Breast medical oncologists’ use of standard prognostic factors to predict a 21-gene Recurrence Score. Oncologist 16(10):1359–1366. doi:10.1634/theoncologist.2011-0048
21. Rayhanabad JA, Difronzo LA, Haigh PI, Romero L (2008) The influence of a gene expression profile on breast cancer decisions. J Surg Oncol 99(6):319–323. doi:10.1002/jso.21244
22. Asad J, Jacobson AF, Estabrook A, Smith SR, Boolbol SK, Feldman SM, Osborne MP, Boachie-Adjei K, Twardzik W, Tartter PI (2008) Does Oncotype DX recurrence score affect the management of patients with early-stage breast cancer? Am J Surg 196(4):527–529. doi:10.1016/j.amjsurg.2008.06.021
23. Rayhanabad JA, DiFrancesco LA, Haigh PI, Romero L (2008) Changing paradigms in breast cancer management: introducing molecular genetics into the treatment algorithm. Am Surg 74(10):887–890
24. Holt SDH, Bennett H, Bertelli G, Valentine WJ, Phillips CJ (2011) Cost-effectiveness evaluation of the Oncotype DX® breast cancer assay in clinical practice in the UK. Paper presented at the San Antonio Breast Cancer Symposium (SABCS), San Antonio, TX, 6–10 December, 2011
25. de Boer RH, Baker C, Speckman D, Mann B (2011) Australian decision impact study: the impact of Oncotype DX Recurrence Score (RS) on adjuvant treatment decisions in hormone receptor positive (HR+), node negative (N0) and node positive (N+) early stage breast cancer (ESBC) in the multidisciplinary clinic (MDC). Paper presented at the San Antonio Breast Cancer Symposium (SABCS), San Antonio, TX, 6–10 December, 2011
26. Yamauchi H, Nakagawa C, Yamashige S, Takei H, Yagata H, Yoshida A, Chien R, Hornberger J, Nakamura S (2011) Decision impact and economic evaluation of the 21-gene Recurrence Score (RS) assay for physicians and patients in Japan. Eur J Cancer 47(Suppl 1):S376

27. Eiermann W, Rezai M, Kummel S, Kuhn T, Warm M, Friedrichs K, Schneeweiss A, Markmann S, Eggemann H, Hilfrich J, Jackisch C, Witzel I, Eidtmann H, Bachinger A, Hell S, Blohmer J (2012) The 21-gene recurrence score assay impacts adjuvant therapy recommendations for ER-positive, node-negative and node-positive early breast cancer resulting in a risk-adapted change in chemotherapy use. Ann Oncol. doi:10.1093/annonc/mds512

28. Joh JE, Esposito NN, Kiluk JV, Laronga C, Lee MC, Loftus L, Soliman H, Boughey JC, Reynolds C, Lawton TJ, Acs PI, Gordan L, Acs G (2011) The effect of Oncotype DX recurrence score on treatment recommendations for patients with estrogen receptor-positive early stage breast cancer and correlation with estimation of recurrence risk by breast cancer specialists. Oncologist 16(11):1520–1526. doi:10.1634/theoncologist.2011-0045

29. Oratz R, Kim B, Chao C, Skrzypczak S, Ory C, Bugarini R, Broder M (2011) Physician survey of the effect of the 21-gene recurrence score assay results on treatment recommendations for patients with lymph node-positive, estrogen receptor-positive breast cancer. J Oncol Pract 7(2):94–99. doi:10.1200/JOP.2010.000046

30. In R, Yamauchi H, Yoshida A, Yagata H, Nakagawa C, Ohde S, Takei H, Nakamura S (2011) Patient satisfaction analysis for decision impact of the 21-gene Recurrence Score (RS) assay. Paper presented at the Global Breast Cancer Conference (GBCC), Seoul, Korea, 6–8 October, 2011

31. Hall PS, McCabe C, Stein RC, Cameron D (2012) Economic evaluation of genomic test-directed chemotherapy for early-stage lymph node-positive breast cancer. J Natl Cancer Inst 104(1):56–66. doi:10.1093/jnci/djr484