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CLINICAL TRIAL

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 Onco*type* 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 Onco*type* 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 Onco*type* DX, 669 controls), all of whom received endocrine therapy with or without chemotherapy. In Onco*type* 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 Onco*type* 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 Onco*type* DX testing, age, tumor size, tumor grade, nodal status, and the interactions between Onco*type* DX testing and the other covariates, Onco*type* 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 Onco*type* 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 · Onco*type* DX · Recurrence Score

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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 Onco*type* 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 Onco*type* 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 a 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 $\leq$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 Onco*type* 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 Onco*type* 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 Onco*type* 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 Onco*type* 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 ("Onco*type* DX") included all patients with N1+, ER+, HER2 negative, BC patients who were diagnosed and had the Onco*type* 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 "Onco*type* DX" group.

Data source

For the Onco*type* 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 Onco*type* 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 Onco*type* DX, 669 controls; Table 1). The vast majority of the Onco*type* 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 Onco*type* 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 Recurrence Score results associated with larger tumors, Spearman correlation; $P = 0.054$).

Table 1 Baseline patient and tumor characteristics

	Oncotype DX group $N = 282$	Controls $N = 669$
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[b,d], *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[e], *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; χ^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; χ^2 test)

[e] $P < 0.0001$ (comparing nodal status distribution; χ^2 test)

Recurrence Score outcomes and treatments received (all patients)

All patients in the Oncotype DX and control groups received endocrine therapy with or without chemotherapy and none received biologic therapy. Overall, the use of adjuvant chemotherapy was lower in the Oncotype DX group compared with controls [24.5 vs. 70.1 %; adjusted odds ratio (OR), 0.16; 95 % Wald confidence limits, 0.11–0.24; adjusted for age, tumor size, grade, and nodal status]. The main source of this observed difference was the very low use of adjuvant chemotherapy in the low Recurrence Score group and the moderate use of adjuvant chemotherapy in the intermediate Recurrence Score group (7.1 and 37.0 %, respectively; Table 3). All patients in the high Recurrence Score group were treated with chemotherapy. The differences in the proportions of patients receiving chemotherapy between the low, intermediate, and high Recurrence Score groups were statistically significant ($P < 0.0001$ for all pairwise comparisons).

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 (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

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) $n = 156$	Intermediate (18–30) $n = 108$	High (≥31) $n = 18$
All ($N = 282$)			
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[a], 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

[a] Tumor size information was not available for 3 patients in the intermediate Recurrence Score group

Table 3 Adjuvant treatment received by Recurrence Score category

	Oncotype DX group								Controls	
	Recurrence Score									
	Low[a] (<18)		Intermediate[a] (18–30)		High[a] (≥31)		All[b]		All[b]	
	$n = 156$		$n = 108$		$n = 18$		$N = 282$		$N = 669$	
Treatment	No.	%	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

(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).

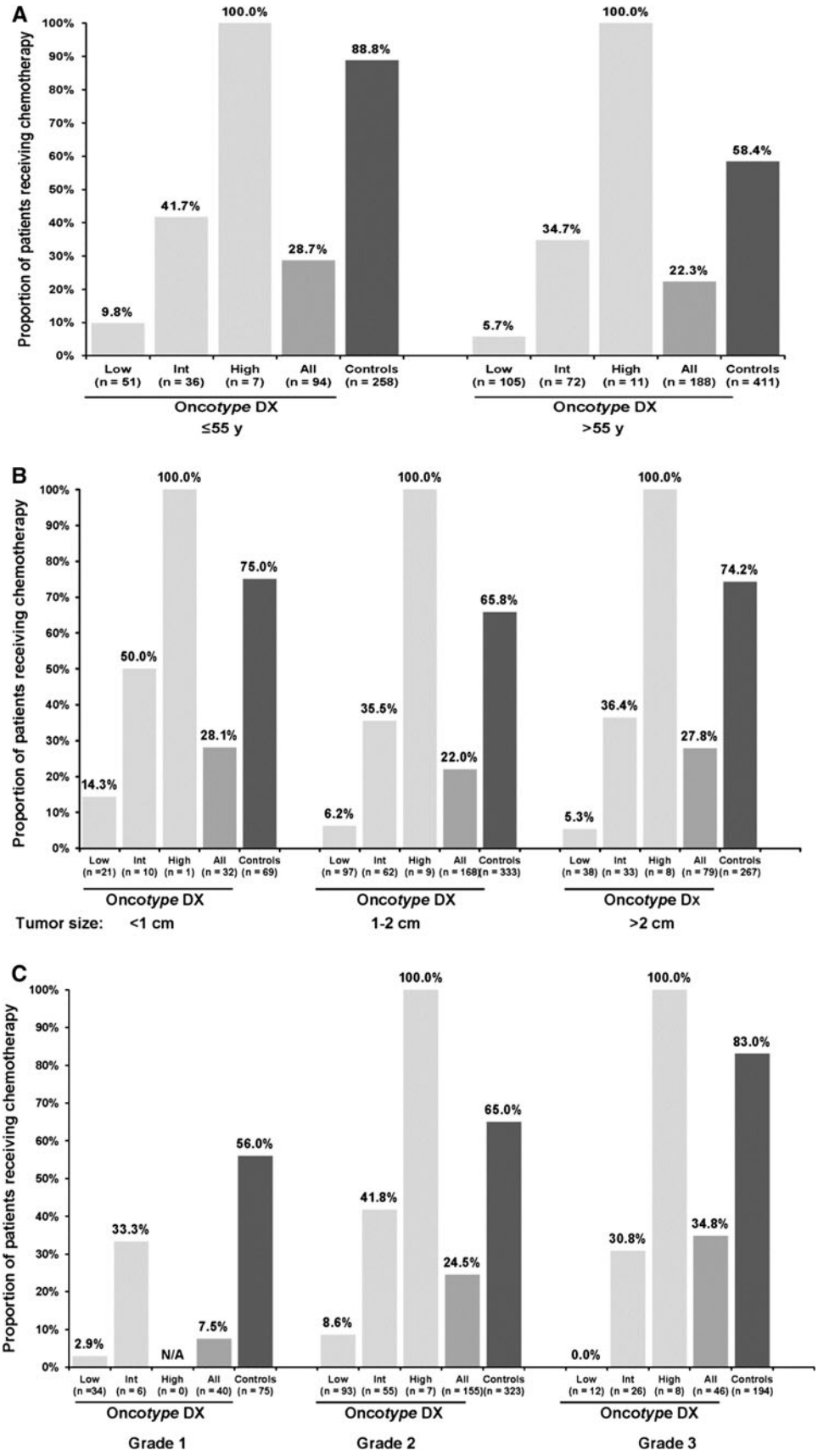

Fig. 1 Proportions of patients receiving chemotherapy by Recurrence Score category and age group (**a**), tumor size (**b**), grade (**c**), and nodal status (**d**). *Int* intermediate, *micromets* micrometastases, *y* year. Only 6 patients were <40 years of age; tumor size information was not available for 3 patients in the intermediate Recurrence Score group; grade information was not applicable/not available for 41 patients in the Onco*type* DX group and 77 controls. In cases of multicentric or bilateral disease, the largest tumor and the highest grade were considered for the analysis

Fig. 1 continued

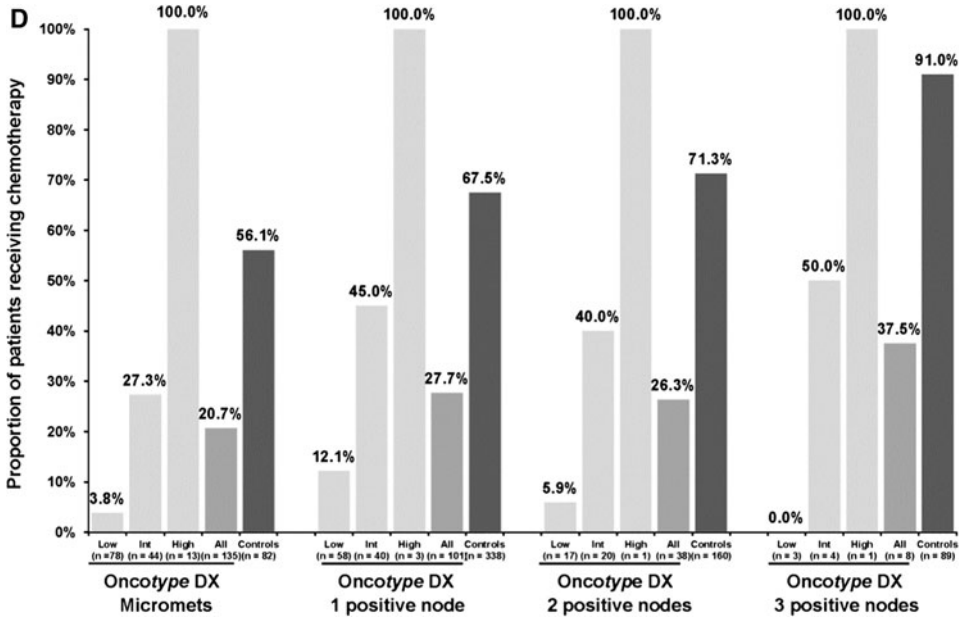

Table 4 Odds ratios for receiving chemotherapy (logistic regression analysis on the entire cohort)

Effect[a]	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

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

Bold values represents statistically significant odds ratios

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 %

(with an adjusted OR of 0.16). 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 N+ 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 Onco*type* 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, Onco*type* 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[a]	Odds ratio	95 % Wald confidence limits	*P* value	Odds ratio	95 % Wald confidence limits	*P* value
	Patients aged 40–55 years			Patients aged >55 years		
Onco*type* 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 Onco*type* DX testing and each of the other covariates were found to be non-significant

Bold values represents 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, Onco*type* 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 Onco*type* DX testing leads to reduced chemotherapy use, and estimated that Onco*type* 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 Onco*type* DX in the N+ ER+ BC population. The only study published to date is a UK-based analysis which showed that using Onco*type* 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 Onco*type* 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 Onco*type* 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 Onco*type* 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 Onco*type* DX patients due to advances in BC awareness and screening over time. Since all of these characteristics impact chemotherapy use (Onco*type* 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 Onco*type* 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 Onco*type* 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 Onco*type* 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 Onco*type* 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 Onco*type* 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, Onco*type* 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. Geffen, M. Steiner, S. Merling, S. Rizel, and N. Lieberman declare no conflict of interest.

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