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Prospective transGEICAM 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

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Background: This study examined the impact of the Recurrence Score (RS) in Spanish breast cancer patients and explored the associations between clinicopathological markers and likelihood of change in treatment recommendations.

Patients and methods: Enrollment was offered consecutively to eligible women with estrogen receptor-positive; human epidermal growth factor receptor 2-negative, node-negative breast cancer. Oncologists recorded treatment recommendation and confidence in it before and after knowing the patient's RS.

Results: Treatment recommendation changed in 32% of 107 patients enrolled: in 21% from chemohormonal (CHT) to hormonal therapy (HT) and in 11% from HT to CHT. RS was associated with the likelihood of change from HT to CHT ($P < 0.001$) and from CHT to HT ($P < 0.001$). Confidence of oncologists in treatment recommendations increased for 60% of cases. Higher tumor grade ($P = 0.007$) and a high proliferative index (Ki-67) ($P = 0.023$) were significantly associated with a greater chance of changing from HT to CHT, while positive progesterone receptor status ($P = 0.002$) with a greater probability of changing from CHT to HT.

Conclusions: Results from the first prospective European study are consistent with published experience and use of the RS as proposed in European clinical practice guidelines and provide evidence on how Onco*type* DX and clinicopathological factors are complementary and patient selection may be improved.

Key words: breast cancer, chemotherapy, estrogen receptor-positive, Oncotype DX, Recurrences Score

introduction

With the traditional instrumentarium of clinical and histopathological markers, decision making in adjuvant treatment of women with estrogen receptor-positive (ER+) early breast cancer remains a difficult task [1, 2]. Routinely, patients receive adjuvant hormonal treatment. Many women are also treated with adjuvant chemotherapy, although a substantial proportion of these will not achieve a further reduction of their risk of recurrence [3]. There is a clear need for better prognostic and predictive tools to identify patients who will derive meaningful clinical benefit from adjuvant chemotherapy.

Research of tumor biology and an evolving knowledge of molecular biologic tumor features have broadened our understanding of breast cancer as a heterogeneous disease and led to the development of new molecular diagnostics such as the multigene assays Mammaprint® (Agendia BV, Amsterdam, The Netherlands), a microarray-based assay assessing the expression of 70 genes [2] and Onco*type* DX® (Genomic Health, Inc., Redwood City, CA). The 21-gene Onco*type* DX

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assay is based on RT-PCR and was specifically developed and optimized to be used in archival formalin-fixed paraffin-embedded tumor tissue [4, 5]. The test can be carried out on routinely processed and archived tumor blocks or slides and measures expression of 5 reference genes and 16 cancer-related genes selected based on correlation of gene expression and risk of distant recurrence in three development studies [6–8]. Using an algorithm based on these clinical studies, the Recurrence Score (RS)—a numeric score between 0 and 100—is calculated [9]. The Onco*type* DX assay quantifies the risk of distant recurrence in patients with ER+ early breast cancer treated with adjuvant hormonal therapy (HT) [9–11] and predicts the magnitude of clinical benefit with additional adjuvant chemotherapy [11, 12]. Its prognostic and predictive significance has been reported in node-negative ER+ breast cancer using tumor specimens from patients enrolled prospectively in studies National Surgical Adjuvant Breast and Bowel Project (NSABP)-B14 [9] and NSABP-20 [12], and, more recently, in node-positive ER+ breast cancer studying tumor specimens originating from the Southwest Oncology Group phase III study S8814 [11]. Recently, results from the Trans-Arimidex, Tamoxifen, Alone or in Combination study confirmed its prognostic and predictive power for adjuvant treatment in node-negative and node-positive patients with the aromatase inhibitor anastrozole [9]. For statistical purposes, three risk groups have been defined: a low-risk group for RS <18, an intermediate-risk group for RS 18–30, and a high-risk group for RS ≥ 31 [9]. However, RS is really a continuous variable quantifying the risk of distant recurrence and chemotherapy benefit for the individual patient [9].

Major scientific societies and study groups have acknowledged the body of evidence and integrated this assay and others into their clinical practice guidelines. In 2007, American Society of Clinical Oncology (ASCO) updated its guidelines and recommended use of RS as a prognostic and predictive marker [13]. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines have integrated the RS into their treatment algorithm for hormone receptor-positive (HR+) human epidermal growth factor receptor 2 (HER2)-negative disease [14]. The St. Gallen 2009 Consensus stated that multigene tests may be used as an additional marker if there is doubt about the indication for adjuvant chemotherapy [1]. Recently, European Society of Medical Oncology (ESMO) issued updated guidelines [2] considering the RS as a prognostic and predictive marker and incorporated the possibility to consider its use to complement pathology assessment and to predict response to adjuvant chemotherapy, in particular in patients with ER+ early stage breast cancer.

Several retrospective and one prospective clinical utility studies have demonstrated that knowledge of RS affects management of patients [15–21], resulting in a revision of treatment recommendations in ∼30% of cases. However, the studies reported to date have been carried out outside Europe. Since there is variation in the use of Onco*type* DX across different NCCN sites [22], it largely remained to be determined whether the overall impact of the test would be similar outside United States. Also, despite European recommendations of integrating the results of genomic platforms with traditional factors, none of the studies had examined the associations between pathological parameters and the likelihood of change in treatment recommendation. This prospective multicenter study was designed by the translational branch of the Spanish Breast Cancer Research Group (transGEICAM) to examine the impact of Onco*type* DX in breast cancer patients and to explore the association between clinicopathological markers and the likelihood of change in treatment recommendations.

patients and methods

This was a prospective multicenter study carried out in centers affiliated with the GEICAM. The study was approved by a central and by institutional ethics committees.

study objectives

The primary objective of the study was to characterize the impact of Onco*type* DX on adjuvant therapy decision making in a cohort of consecutive patients with node-negative ER+ HER2-negative breast cancer. Secondary study objectives were to assess the confidence of medical oncologists in their treatment recommendation before and after Onco*type* DX testing, to explore the relationship between routine clinicopathological characteristics and the likelihood of change in adjuvant therapy recommendation after testing, and to correlate results for ER and progesterone receptor (PR) status with those obtained by quantitative messenger RNA measurements provided by the Onco*type* DX assay. ER and PR were routinely assessed by immunohistochemistry (IHC) using anti-ERα specificity protein 1 clone antibody (from Dako in four centers; and from Ventana-Roche in two) and anti-PR PgR636 clone antibody (Dako, Glostrup, Denmark) in four centers and 1E2 clone (Ventana-Roche, Tucson, Arizona) in two centers, following ASCO/College of American Pathologists (CAP) guidelines [23]. HER2 status was determined by IHC using Herceptest (Dako) in all patients and confirmed by FISH when indicated (Pathvysion, Abbott in two centers; PharmaDX, Dako, in two centers), following ASCO/CAP recommendations [24].

eligibility

Enrollment was offered consecutively to all eligible women by the participating medical oncologists. Women had to have operable breast cancer, ER+, HER2 negative by IHC or FISH, tumor size of ≥1 cm (T1, 2, 3 excluding those with dermal involvement) or <1 cm if at least one histological unfavorable characteristic (high histological grade, angiolymphatic invasion, and high proliferation index), histologically verified negative lymph nodes, age ≥18 years, good performance status (Eastern Cooperative Oncology Group 0–1, Karnofsky performance status ≥70), no contraindication for receiving systemic chemohormonal therapy, and had to be able to give informed consent in writing.

medical oncologists

Nineteen oncologists from six GEICAM centers participated in the study. They had an approved specialization were mainly focused on breast cancer and were members of Spanish Society of Medical Oncology and GEICAM. Twelve had at least 10 years of clinical practice.

physician questionnaires

Each participating medical oncologist completed a pretest questionnaire specifically developed for this study recording the initial treatment recommendation of the oncologist and her/his confidence in this recommendation before knowing the patient's RS. After knowledge of RS results, oncologists completed a post-RS follow-up questionnaire stating their final treatment recommendation and their confidence in it.

statistical analyses

Sample size was determined on the basis of published experience for changes in adjuvant treatment recommendations associated with the use of Onco*type* DX with reported change rates of 21%–44%. It was assumed that the change rate of treatment recommendations (from an initial recommendation for chemohormonal to hormonal treatment and vice versa) would be at minimum 25%. A sample size of at least 100 patients was needed to estimate this change rate with a 95% confidence interval (CI) of width ±9%.

Descriptive statistics were used to summarize patient and tumor characteristics and changes in oncologists' treatment recommendations and in their confidence in their treatment recommendations. Logistic regression was used to explore the associations between age, tumor size, tumor grade [25], PR status, and proliferative index as defined by Ki-67 [26] and the likelihood of change from hormonal to chemohormonal and from chemohormonal to hormonal treatment after Onco*type* DX testing. Similar analyses were carried out for the RS.

The correlation between percentage of positively stained cells by IHC at local pathology departments at participating centers and by quantitative single gene reporting as provided by the Onco*type* DX assay was evaluated for ER and PR with the Pearson correlation coefficient.

results

patient and tumor characteristics

One hundred and seven patients were enrolled between August 2009 and June 2010. Actual accrual period ranged between 6 and 8 months in different hospitals. The estimated number of new breast cancers seen by participating doctors during the study was ∼723 cases; the estimated number of patients fitting the criteria for the study was ∼123, slightly superior than the actual number of patients included. Two sites had a selection bias of 10%–20% for women they felt candidates to chemotherapy plus HT and therefore were not offered to participate in the study. Thus, based on our estimations, the majority of patients fitting the criteria were actually entered in the study. Complete patient and tumor characteristics and the distribution of RS are listed in Table 1. Sixty-two (58%) patients had a low RS of <18, 35 (33%) had an intermediate RS of 18–30 and 10 (9%) had a high RS of ≥31.

treatment recommendations before and after knowledge of RS

Changes in treatment recommendations from pre- to postknowledge of Onco*type* DX results are summarized in Table 2. Before knowledge of RS, and based solely on classical clinicopathological factors, adjuvant chemohormonal therapy (CHT) would have been recommended to 39 of the 107 women (36%) and HT alone to the remaining 68 women (64%). This would have resulted in treating with CHT for 22 (35%) of low risk, 9 (26%) of intermediate risk, and 8 (80%) of high-risk women (Table 2). However, the actual treatment option recommended after knowledge of RS results was CHT in a smaller number of women ($n = 29$; 27%) and the recommendation was highly consistent with the expected use of CHT according to RS grouping; 2/62 patients (3%) with low RS, 17/35 (49%) with intermediate RS, and in all 10 patients with high RS.

Treatment recommendations were changed in 34 patients (32%; 95% CI 26% to 34%) after results of individual RS were available. For 22 patients (21%; 95% CI 19.6% to 21.6%), the initial recommendation was revised from chemohormonal to HT and for 12 individuals (11%; 95% CI 10.6% to 11.8%), from HT to CHT. In the low RS group, treatment recommendations changed for 20 of 62 patients (32%). For all of these patients, the change was from an initial recommendation for CHT to HT. In two women with pathological tumor size 2 tumors and a low RS of 13 and 14, the pretest recommendation for CHT was not changed. Among the 10 patients with high RS, 2 had a change in treatment plan, both from HT to CHT. A total of 12 of the 35 women with intermediate risk had a change in recommendation (10 from HT to CHT and 2 from CHT to HT). Women with intermediate RS who received HT ($N = 18$) had a mean RS of 20 (range: 18–29) and those who received CHT ($N = 17$) had a mean RS of 21 (range 18–27) ($P = 0.258$). Albeit the precise reasons for the change in recommendations are not evident, we feel that the potential benefit of chemotherapy in this subset of women lead to an increase in CHT recommendations after the test in intermediate-risk women.

Table 1. Baseline characteristics of patients and tumors

Characteristics		*N* (%)	Mean RS	RS < 18, *n* (%)	RS 18–30, *n* (%)	RS ≥ 31, *n* (%)
Total		107 (100)	17.5	62 (58)	35 (33)	10 (9)
Age (years)	<50	40 (37)	17.5	23 (58)	15 (38)	2 (5)
	≥50	67 (62)	17.5	39 (58)	20 (30)	8 (12)
Tumor size	pT1	91 (85)	16.9	55 (60)	28 (31)	8 (9)
	pT2	16 (15)	20.3	7 (44)	7 (44)	2 (13)
Tumor grade	Low	37 (35)	14.5	25 (68)	11 (30)	1 (3)
	Intermediate	46 (43)	18.2	25 (54)	17 (37)	4 (9)
	High	20 (19)	22.2	9 (45)	6 (30)	5 (25)
	Unknown	4 (4)	14.0	3 (75)	1 (25)	0 (0)
Progesterone receptor	Negative	16 (15)	27.6	3 (19)	7 (44)	6 (38)
	Positive	90 (84)	15.6	59 (66)	27 (30)	4 (4)
	Unknown	1 (1)	26.0	0 (0)	1 (100)	0 (0)
Ki-67 (%)	<20%	61 (57)	14.5	43 (71)	16 (26)	2 (3)
	≥20%	29 (27)	22.1	14 (48)	9 (31)	6 (21)
	Unknown	17 (16)	20.4	5 (29)	10 (59)	2 (12)

RS, Recurrence Score; pT, pathological tumor size.

Table 2. Oncologists' treatment recommendation before and after knowledge of RS

Pre- to post-RS treatment recommendation	Low RS (<18) $N = 62$, n (%)	Intermediate RS (18–30) $N = 35$, n (%)	High RS (>30) $N = 10$, n (%)	Total $N = 107$, n (%)
Treatment plan changed	20 (59)	12 (35)	2 (6)	34 (32)
HT to CHT	0 (0)	10 (83)	2 (17)	12 (11)
CHT to HT	20 (91)	2 (9)	0 (0)	22 (21)
Treatment plan not changed	42 (58)	23 (32)	8 (11)	73 (68)
CHT to CHT	2 (12)	7 (41)	8 (11)	17 (16)
HT to HT	40 (71)	16 (29)	0 (0)	56 (52)

RS, Recurrence Score; HT, hormonal therapy.

RS was significantly associated with the likelihood of change from HT to CHT ($P < 0.001$) and from CHT to HT ($P < 0.001$). All women except one followed posttest recommendation. This patient refused to have chemotherapy.

medical oncologists' confidence in treatment recommendation before and after knowledge of RS

A total of 103 cases were evaluable regarding medical oncologists' confidence in their treatment recommendation before and after knowledge of RS. Results are summarized in Table 3. The confidence of the medical oncologists in their treatment recommendation increased in 60% and decreased in 7% of cases, while it had no discernible impact on their confidence in 33 %.

association between clinicopathological variables and the likelihood of change in treatment recommendation after knowledge of RS results

We carried out univariate analyses for clinicopathological baseline characteristics and the likelihood of a change in treatment recommendation before and after Onco*type* DX testing in an attempt to identify predictors for a treatment shift from CHT to HT (Table 4) and from HT to CHT (Table 5). In women with a HT recommendation before testing, treatment shifted to CHT in 18% of cases. Higher tumor grade and a high proliferative index (Ki-67) were significantly associated with a greater chance of changing from HT to CHT. In women with CHT recommendation before testing, treatment shifted to HT alone in 56% of cases. Positive PR status was significantly associated with a greater probability of changing from CHT to HT.

concordance between determination of ER and PR status by IHC versus quantitative single gene reporting provided by Onco*type* DX

The correlation between detection of percentage of positively stained cells by IHC at participating local pathology departments and for quantitative single gene reporting provided by the Onco*type* DX assay is illustrated in Figure 1 for ER and PR. The correlation for PR (Pearson $r = 0.78$) was relatively high but relatively low for ER (Pearson $r = 0.34$). Also, there was a high concordance for detection of HER2 status and only in two cases, the results of the single gene reporting by RT-PCR were equivocal as opposed to HER2 negativity detected by IHC or FISH.

Table 3. Medical oncologists' confidence in their treatment recommendations pre- and posttest

Confidence pretest	Confidence posttest			
	Low	Intermediate	High	Complete
Low	0	6	5	2
Intermediate	1	4	24	11
High	2	3	27	14
Complete	0	0	1	3

Table 4. Univariate analysis for association between clinicopathological variables and likelihood of change from CHT to HT after Onco*type* testing

Characteristics		Change from CHT to HT	
		n (%)	P value
Total ($N = 39$)		22 (56)	
Median age ($N = 39$), years	<50 ($n = 17$)	11 (65)	0.358
	≥50 ($n = 22$)	11 (50)	
Tumor size ($N = 39$)	pT1 ($n = 28$)	18 (64)	0.114
	pT2 ($n = 11$)	4 (36)	
Tumor grade ($N = 37$)	Low ($n = 9$)	4 (44)	0.424
	Intermediate ($n = 16$)	11 (69)	
	High ($n = 12$)	6 (50)	
Progesterone receptor ($N = 39$)	Negative ($n = 9$)	1 (11)	0.002
	Positive ($n = 30$)	21 (70)	
Ki-67 ($N = 34$), %	<20 ($n = 18$)	11 (61)	0.774
	≥20 ($n = 16$)	9 (56)	

HT, hormonal therapy; pT, pathological tumor size.

discussion

This is the first study on the impact of the Onco*type* DX assay on clinical decision making in early breast cancer in a European patient population. It confirms and extends the results of the first prospective clinical impact study reported for the assay by Lo et al. [20].

In this Spanish study, treatment recommendations changed for 31.8% of the women after the results of the assay were known. Treatment recommended posttesting was mainly driven by RS results. The most common overall change was from a recommendation of CHT to HT alone in 20.6% of

cases. In the prospective USA study published by Lo et al. [20], physician treatment recommendations changed in 31.5% of cases with a rate of 22.5% for a shift from CHT to HT. The authors also reported on consistency of postassay treatment recommendation with the RS.

Similar to the USA study, we explored the confidence of medical oncologists in their treatment recommendation and found that it improved in 60% of the cases after the RS, while Lo reported on an increase of 76%. However, a study carried out in 11 NCCN centers found an overall use of Onco*type* DX in ~22% of women with HR+ disease and 38% for those with HR+ node-negative breast cancer [22]. Thus, the oncologists in the Lo study routinely ordered the test in their clinical practice outside the study, while Onco*type* DX was not yet part of clinical routine for the Spanish oncologists.

Few studies have gone beyond testing the impact of Onco*type* DX on treatment recommendations. Our study is the first that explored the association between histopathological parameters and the probability of change when being tested with the 21-gene assay. Positive PR status was significantly associated with a greater chance of changing to HT. Intermediate and high tumor grade and a high proliferative index (Ki-67) were significantly associated with a greater chance of changing to CHT. Presence of a good prognostic baseline parameter such as positive PR status or presence of less favorable prognostic markers such as high tumor grade predicting for a specific treatment shift may have potential for better individualizing testing with the 21-gene assay. Looking at an overall use of the Onco*type* DX assay in up to 37% of women reported for some institutions [22], it is desirable to develop strategies that can enhance the cost–benefit ratio and thus make testing more cost-effective. Looking at sociological and clinicopathological factors, Hassett et al. [22] explored patterns and predictors of the use of the 21-gene assay and found e.g. for women with high grade tumors, a higher likelihood of being tested as compared with women with low grade tumors. A retrospective study from Israel found that standard clinicopathologic features could generally not predict the RS in ER+ node-negative patients but reported on an association of high tumor grade and low PR status with a high RS [27].

While we have observed statistically significant associations between a few clinicopathological variables and the likelihood of change in treatment decision after Onco*type* DX testing, we acknowledge that some of the subgroups are relatively small (e.g. of the 68 patients originally recommended for HT, only 8 patients had high tumor grade and only 13 had a high proliferative index), so the estimated probabilities of change have very wide CIs i.e. the 95% CI for the change rate from HT to CHT was 15.7% and 84.3% for high tumor grade, 9.1%

Table 5. Univariate analysis for association between clinicopathological variables and likelihood of change from HT to CHT after Oncotype testing

Characteristics		Change from CHT to HT	
		n (%)	*P* value
Total (*N* = 68)		12 (18)	
Median age (*N* = 68), years	<50 (*n* = 23)	6 (26)	0.192
	≥ 50 (*n* = 45)	6 (13)	
Tumor size (*N* = 68)	pT1 (*n* = 63)	10 (16)	0.173
	pT2 (*n* = 5)	2 (40)	
Tumor grade (*N* = 66)	Low (*n* = 28)	1 (4)	0.007
	Intermediate (*n* = 30)	7 (23)	
	High (*n* = 8)	4 (50)	
Progesterone receptor (*N* = 67)	Negative (*n* = 7)	1 (14)	0.792
	Positive (*n* = 60)	11 (18)	
Ki-67 (*N* = 56), %	<20 (*n* = 43)	3 (7)	0.023
	≥20 (*n* = 13)	4 (31)	

HT, hormonal therapy; pT, pathological tumor size.

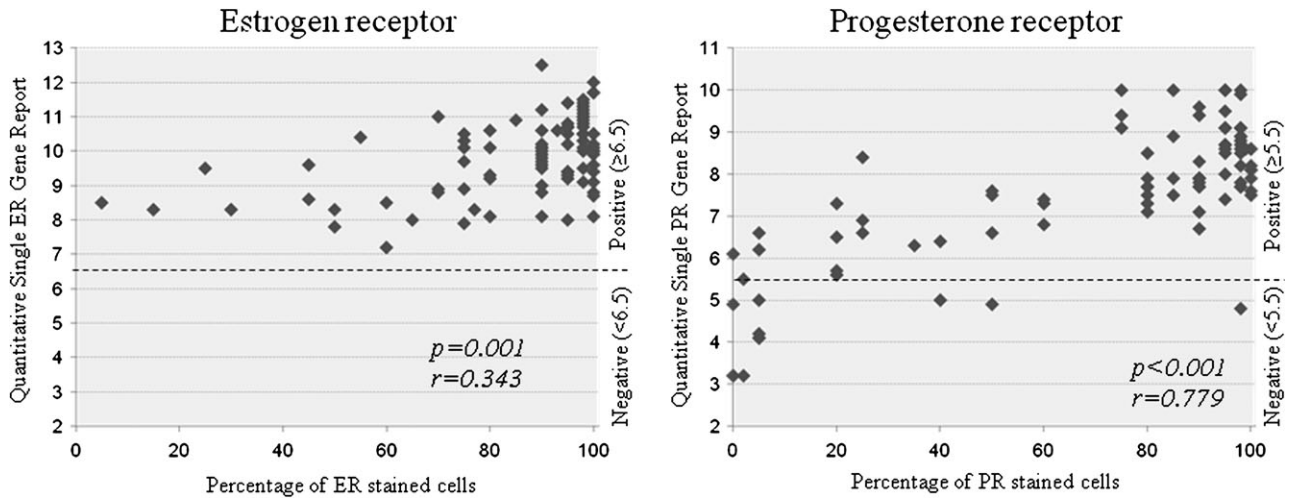

Figure 1. Correlation between percentage of expression by immunohistochemistry (IHC) and quantitative single gene report for estrogen receptor (ER) and progesterone receptor (PR) by Onco*type* DX. Legend to figure: The correlation between percentage of positively stained cells by IHC at local pathology departments at participating centers and by quantitative single gene reporting as provided by the Onco*type* DX assay was evaluated for ER and PR with the Pearson correlation coefficient.

and 61.5% for high proliferative index, and the 95% CI was 0.3% and 48.2% for the change rate from CHT to HT for PR-negative patients. Larger studies are needed to confirm these results and yield estimates with adequate precision.

Moreover, the RS has been shown to provide additional prognostic and predictive information beyond classical clinical and histopathologic criteria [9, 10, 12, 28]. Some women whose tumors had an intermediate or high tumor grade had low RS predicting low risk of distant recurrence and a minimal benefit of additional chemotherapy [7, 29]. It will be key to integrate RS and clinicopathological factors to optimize guiding adjuvant treatment decision making and avoid under and, more often, overtreatment of patients. One study has reported on the development of a formal tool called *RSPC* integrating RS and traditional clinicopathologic factors such as age, tumor size, and tumor grade to guide informed treatment decisions [30].

Also, it may not be cost-effective at first glance if a shift from HT to CHT occurs in a considerable proportion of patients. However, it needs to be pointed out that this should result in more lives saved besides the fact that the cost for treating metastatic disease is high. Pharmacoeconomic calculations based on the results reported by Lo [31] found that the average quality-adjusted life-years gained exceeded 0.2 years and was associated with a direct medical savings of $2,099 for chemotherapy drugs, $902 for supportive care, $1,049 for management of adverse events, and $230 resulting from fewer recurrences. Including the cost of the assay, the average total direct medical savings exceeded $300 dollars per patient tested.

A limitation one can point out regarding the Onco*type* DX assay and our study is that the assay's prognostic validation has been carried out based on adjuvant tamoxifen treatment and its validation of the prediction of chemotherapy benefit is based on methotrexate and fluorouracil or combination chemotherapy with cyclophosphamide, methotrexate, and fluorouracil. However, data recently published on patients treated with anastrozole confirmed the prognostic value of the RS for adjuvant treatment with an aromatase inhibitor [10]. Its predictive significance was shown for chemotherapy with combination chemotherapy with cyclophosphamide, doxorubicin, and fluorouracil in a node-positive patient population [11] and a neoadjuvant study suggests that this is also likely for taxane-based chemotherapy [32]. Results of current prospective studies such as Trial Assessing IndiviuaLized Options for Treatment for breast cancer (TAILORx) and the German Plan B study will provide additional data regarding the assay's predictive significance for a number of contemporary chemotherapy regimens.

Finally, it is worth mentioning that there was a high concordance between ER and PR testing by IHC, as well as for HER2 testing, at local pathology departments and for quantitative single gene reporting provided by the Onco*type* DX assay. This has been reported by other groups accordingly [33].

In conclusion, these results from a European setting are in line with those reported on the impact of the Onco*type* DX assay from USA studies and are consistent with the potential use of the RS as proposed in European recommendations i.e. St. Gallen Expert Consensus and ESMO clinical practice guidelines. Results also illustrate how Onco*type* DX and traditional clinicopathological factors are complementary in supporting change in treatment recommendations and suggest how patient selection may be improved if necessary.

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disclosures

JA participation in advisory board and invited speaker for Genomic Health Inc., JMC, JP, EA, AL, JAGS, RC, MM participation in advisory boards for Genomic Health Inc., IF scientific advisor to Genomic Health Inc., and AG, MRB, OB, VF, AR, BB, MMG, MLL, ASM, IT, FR have declared no conflicts of interest.

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