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RESEARCH ARTICLE

Prospective, multicenter study on the economic and clinical impact of gene-expression assays in early-stage breast cancer from a single region: the PREGECAM registry experience

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Abstract

Introduction The aim of this study is to evaluate the cost-effectiveness and impact of gene-expression assays (GEAs) on treatment decisions in a real-world setting of early-stage breast cancer (ESBC) patients.

Methods This is a regional, prospective study promoted by the Council Health Authorities in Madrid. Enrolment was offered to women with estrogen receptor-positive, human epidermal growth factor receptor 2-negative, node-negative or micrometastatic, stage I or II breast cancer from 21 hospitals in Madrid. Treatment recommendations were recorded before and after knowledge of tests results. An economic model compared the cost-effectiveness of treatment, guided by GEAs or by common prognostic factors.

Results 907 tests (440 Oncotype DX® and 467 MammaPrint®) were performed between February 2012 and November 2014. Treatment recommendation changed in 42.6% of patients. The shift was predominantly from chemohormonal (CHT) to hormonal therapy (HT) alone, in 30.5% of patients. GEAs increased patients' confidence in treatment decision making. Tumor grade, progesterone receptor positivity and Ki67 expression were associated with the likelihood of change from CHT to HT ($P < 0.001$) and from HT to CHT ($P < 0.001$). Compared with current clinical practice genomic testing increased quality-adjusted life years by 0.00787 per patient and was cost-saving from a national health care system (by 13.867€ per patient) and from a societal perspective (by 32.678€ per patient).

Conclusion Using GEAs to guide adjuvant therapy in ESBC is cost-effective in Spain and has a significant impact on treatment decisions.

Keywords Breast cancer · Gene-expression profiling · Cost analysis · Quality-adjusted life years

Introduction

Breast cancer (BC) is the most frequent cancer among women with an estimated 1.09 million new cases diagnosed in 2018 (32,825 in Spain) [1]. Half of these women present with estrogen-receptor (ER) positive, human epidermal growth factor receptor-2 (HER2) negative disease, and negative lymph nodes.

Adjuvant treatments for this population include combined chemohormonal therapy (CHT) or hormonal therapy (HT) alone. Adjuvant chemotherapy (CT) is elected on the basis of risk of relapse, estimated by considering a number of prognostic factors including tumor size, grade, Ki67 expression, presence or absence of lymphovascular invasion and lymph node involvement [2]. Before the arrival of gene-expression assays (GEAs) guidelines recommend adjuvant CT in most cases, despite the fact that most of these patients obtain no benefit from CT. Thus, more reliable predictors of recurrence would refine treatment selection.

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In this regard, GEAs have shown a clear prognostic ability and have been incorporated in treatment-directing predictive models. Oncotype DX® measures gene expression by real-time polymerase chain reaction (PCR) using formalin-fixed paraffin-embedded (FFPE) tissue. The test yields a recurrence score (RS) that acts as a continuous variable but is grouped into low-, intermediate- and high-risk categories [3]. MammaPrint®, performed either on fresh or FFPE tissue, uses a microarray-based technology yielding two prognostic groups: low and high risk [4]. Several prospective studies demonstrate that the implementation of these tests impact on physician's adjuvant decision making, resulting in a change of treatment recommendation in up to 30% of cases [5-10]. Evidence suggests GEAs are likely cost-effective and even cost-saving relative to current clinical-driven approaches [11]. Clearly the greatest challenge ahead is to define the appropriate role of these tests in clinical practice and treatment decision making.

In 2012, the health authorities in Madrid, a Spanish region with approximately 6,000,000 inhabitants and around 3000 new BC diagnoses per year, promoted a prospective program aimed at evaluating the impact of GEAs in ESBC management. The program, called "Predictores Genómicos en Cáncer de Mama de la Comunidad de Madrid" (PREGECAM), was implemented in all public hospitals in Madrid.

The primary aims of PREGECAM were two: (1) to prospectively evaluate the impact of Oncotype DX® and MammaPrint® on adjuvant decision making in BC patients in Madrid and (2) to assess cost-effectiveness compared with traditional prognostic factors. Secondary study objectives were (1) to examine the association between clinicopathological markers and the likelihood of change in treatment recommendations, and (2) to explore patient perceptions of GEAs and their impact on adjuvant treatment decisions.

Material and methods

This prospective, multicenter program included all eligible patients treated in any of the 21 public hospitals located in the Madrid region (Online resource 1). Approval from a central ethics committee was obtained before study initiation. All eligible patients provided written informed consent prior to the inclusion in the study.

Patients

Enrolment was offered consecutively to all eligible women presenting with operable BC, ER + /HER2− by immunohistochemistry (IHQ) or fluorescence in situ hybridization (FISH), tumor size of ≥ 1 cm (T1, 2, 3, excluding those with dermal involvement) or < 1 cm with at least one histological unfavourable characteristic (intermediate or high histological grade, lymphovascular invasion or Ki67 > 13%). Further inclusion criteria were good performance status (PS 0, 1), a life expectancy of more than 5 years and no contraindication for CT.

Questionnaires

Before a genomic test was authorized, each participating medical oncologist completed a pre-test questionnaire (Online resource 2) recording their initial treatment recommendation based solely on standard prognostic factors. In addition, oncologists ordered either Oncotype DX® Breast Recurrence Score Assay; Genomic Health, Inc., Redwood City, CA. or MammaPrint®; AGENDIA BV; Amsterdam, NL1098 XH, (the two GEAs available in Spain at that moment) according to their preference. Both tests were performed using FFPE BC tissue.

After receiving test results, oncologists completed a post-test questionnaire (Online resource 3) stating their final treatment recommendation. Treatment recommendations had to be detailed in terms of CHT or HT and included the specific agents actually administered.

Patients also completed a questionnaire assessing their knowledge and personal opinion regarding the role of GEAs in the treatment of ESBC (Online resource 4).

Pharmacoeconomic analysis

An economic model was developed using a decision tree (until the end of CT) and a Markov model containing three mutually exclusive health states (no recurrence, recurrence, and death from cancer) (Fig. 1) over a time horizon of 10 years. The probabilities of treatment recommendation before and after GEAs results were obtained from PREGECAM. The rest of probabilities (including risk of CT toxicity, recurrence, and death) and utilities were obtained from literature review [12-22]. The medical charts of 132 patients in PREGECAM were reviewed to quantify the health care resources associated to CT administration. A random sample of 68 patients who received CT in a single institution (Hospital Gregorio Marañón) were also interviewed to estimate indirect and direct non-health care costs related to CT. Costs of health care resources were retrieved from social security public records and literature review [23-30]. Deterministic and probabilistic sensitivity analyses were performed.

Statistical analysis

All study variables were summarized using descriptive statistics. Chi-squared test and unpaired sample *t* tests were used to evaluate the association between categorical and quantitative

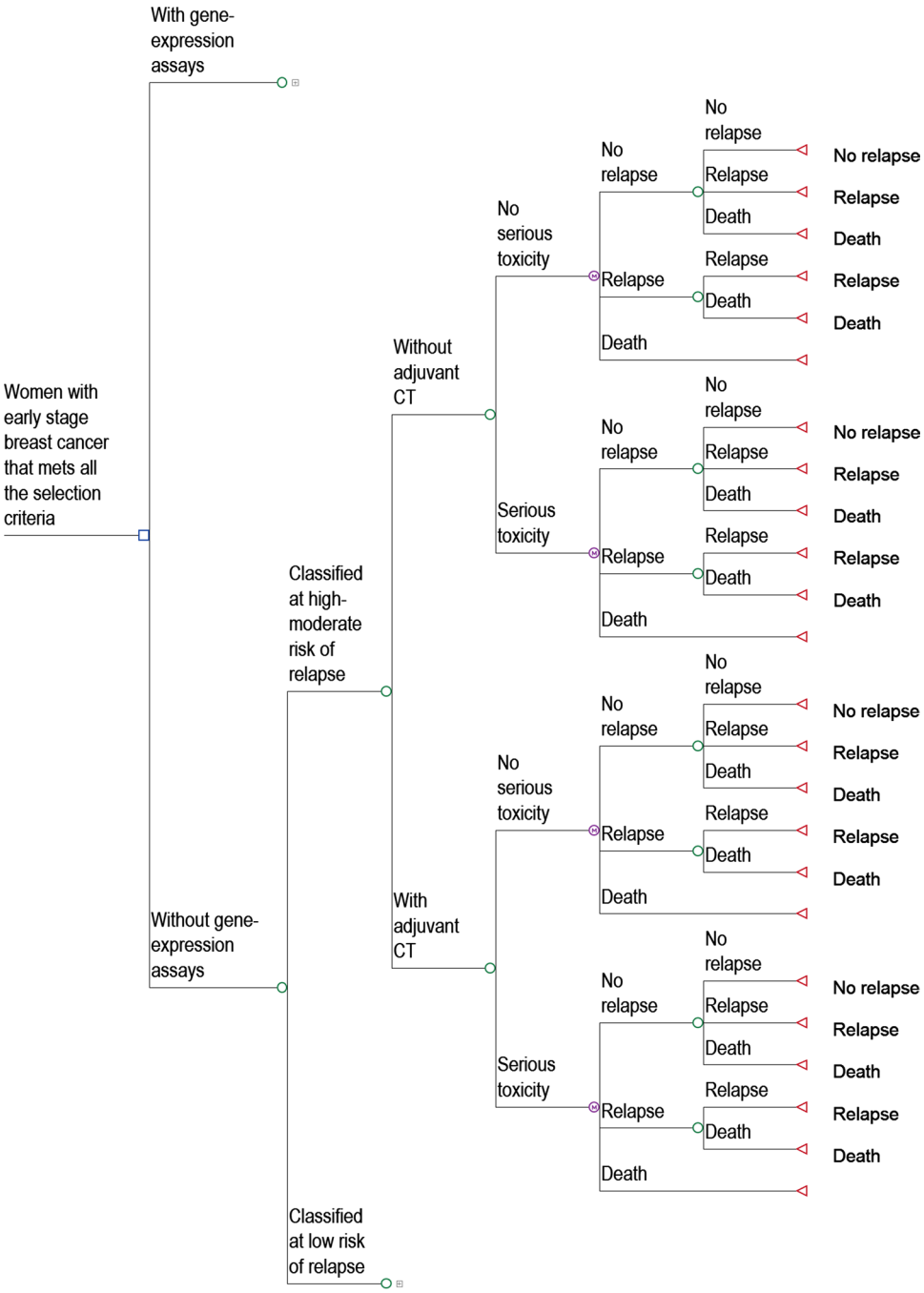

Fig. 1 Economic model: decision tree until the end of CT and a Markov model with a time horizon of 10 years

variables. Data on pre- to post-test treatment recommendation were compared using the McNemar's test. Logistic regression was used to explore the association between clinicopathological indicators and the likelihood of change in treatment recommendation. All statistical analyses were performed using SPSS, version 19 for Windows (SPSS Inc, Chicago, IL, USA) with significance determined at a two-side α level of ≤ 0.05.

Results

Demographics

Between February 2012 and November 2014, a total of 953 patients were enrolled. Nine-hundred and seven patients were fully assessable and are included in this study.

Table 1 Patient characteristics

Characteristics	*N* (%)
All assessable patients	907 (100)
Age (years)	
Median	54
Range	18–77
Tumor size	
pT1	712 (78.5)
pT2	187 (20.6)
pT3	2 (0.2)
Unknown	6 (0.7)
Tumor grade	
Low	193 (21.3)
Intermediate	577 (63.6)
High	134 (14.8)
Unknown	3 (0.3)
Progesterone receptor	
Negative	82 (9.0)
Positive	819 (90.3)
Unknown	6 (0.7)
Ki67 (%)	
< 20%	529 (58.3)
≥ 20%	364 (40.1)
Unknown	14 (1.5)
Lymph nodes	
N_0	719 (79.3)
N_{mic}	173 (19.1)
Unknown	15 (1.7)
LVI	
Negative	727 (80.2)
Positive	109 (12.0)
Unknown	71 (7.8)

pT pathological tumor size, N_0 negative lymph node, N_{mic} lymph node micrometastasis, *LVI* lymphovascular invasion

Patient and tumor characteristics are listed in Table 1. Oncotype DX® was performed in 440 (48.6%) patients. RS distribution showed 54.1% of tumors were low risk (RS < 18), 38.2% were intermediate risk (RS 18 to 30) and 7.7% were high risk (RS ≥ 31). MammaPrint® was performed in 467 patients (51.4%). Recurrence risk was low in 64.6% of cases and high in the remaining 36.4%.

Treatment recommendations before and after GEAs results

Changes in treatment recommendations from pre- to post-test results are summarized in Tables 2 and 3.

Initial treatment recommendation was revised in 42.6% of all assessable patients. The greatest change was from a pre-test recommendation of CHT to a post-test recommendation of HT in 277 (30.5%) patients. Remarkably, 109 (12%) patients with a pre-test recommendation of HT were finally allocated to CHT.

Treatment recommendations were changed in 196 of the 440 (44.5%) women tested with Oncotype DX®. For 152 (34.5%) patients the initial recommendation was revised from CHT to HT and for 44 (10%) individuals from HT to CHT. The post-RS assay treatment recommendation was consistent with the RS.

Likewise, treatment recommendations were changed in 190 of the 467 (40.7%) women tested with MammaPrint®. For 125 (26.8%) patients the initial recommendation was revised from CHT to HT and for 65 (13.9%) individuals from HT to CHT. The post-assay recommendation remained consistent with the risk results.

The recurrence risk provided by both GEAs was significantly associated with the likelihood of change in treatment recommendations ($P < 0.001$).

Cost-effectiveness analysis

According to deterministic analyses, costs per patient from a national health system and from a societal perspective, compared to current clinical practice were lower with GEAs, by 13,867€ and 32,678€ respectively. Reallocation of adjuvant CT based on test results was associated with an improvement of 0.00787 quality-adjusted life years (QALYs) per patient. Overall, Onco*type* Dx and MammaPrint® were found to dominate over standard care. According to probabilistic results,

Table 2 Treatment recommendation before and after Oncotype DX® test results

Pre- to post-Oncotype DX® treatment recommendation	Low RS (< 18) *N* = 238 *n* (%)	Intermediate RS (18–30) *N* = 168 *n* (%)	High RS (> 30) *N* = 34 *n* (%)	Total *N* = 440 *n* (%)
Treatment plan changed	127 (65)	63 (32)	6 (3)	196 (45)
HT–CHT	0 (0)	38 (86)	6 (14)	44 (10)
CHT–HT	127 (84)	25 (16)	0 (0)	152 (35)
Treatment plan not changed	111 (45)	105 (43)	28 (11)	244 (55)
CHT–CHT	7 (6)	85 (71)	28 (23)	120 (27)
HT–HT	104 (84)	20 (16)	0 (0)	124 (28)

RS recurrence score, *HT* hormone therapy, *CHT* chemohormonal treatment

Table 3 Treatment recommendation before and after MammaPrint® test results

Pre- to post-MammaPrint® treatment recommendation	Low risk *N* = 297 *n* (%)	High risk *N* = 170 *n* (%)	Total *N* = 467 *n* (%)
Treatment plan changed	125 (66)	65 (34)	190 (41)
HT–CHT	0 (0)	65 (100)	65 (14)
CHT–HT	125 (100)	0 (0)	125 (28)
Treatment plan not changed	172 (62)	105 (38)	277 (59)
CHT–CHT	4 (4)	105 (96)	109 (23)
HT–HT	168 (100)	0 (0)	168 (36)

HT hormone therapy, *CHT* chemohormonal treatment

the probability of saving costs with GEAs is 100%, both from a national health system by 13,920€ (95% CI 11,697€; 17,218€), and from a societal perspective, by 32,793€ (95% CI 28,432€; 37,827€) whereas the probability of cost-effectiveness (for a willingness to pay 30,000€ per QALY gained) is 78.5% and 78% respectively (Figs. 2 and 3).

Association between clinicopathological variables and the likelihood of change in treatment recommendation after GEAs results

In attempt to identify predictors for treatment shift from CHT to HT and from HT to CHT, a logistic regression analysis was performed between clinicopathological baseline characteristics and the likelihood of change in treatment recommendation before and after gene-expression testing.

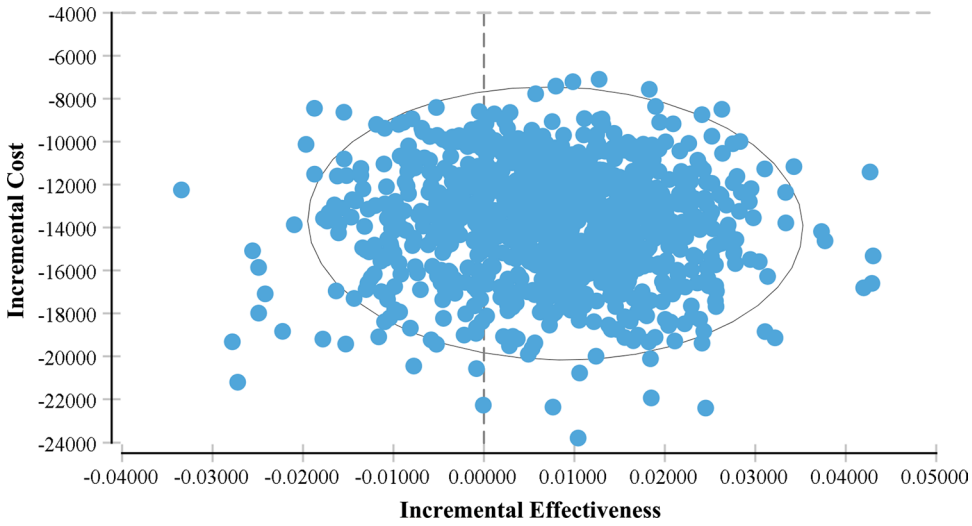

Fig. 2 Probabilistic analysis. Cost-effectiveness plane. The probability of cost-effectiveness from a national health system perspective is 78.5%. *QALYS* quality-adjusted life years

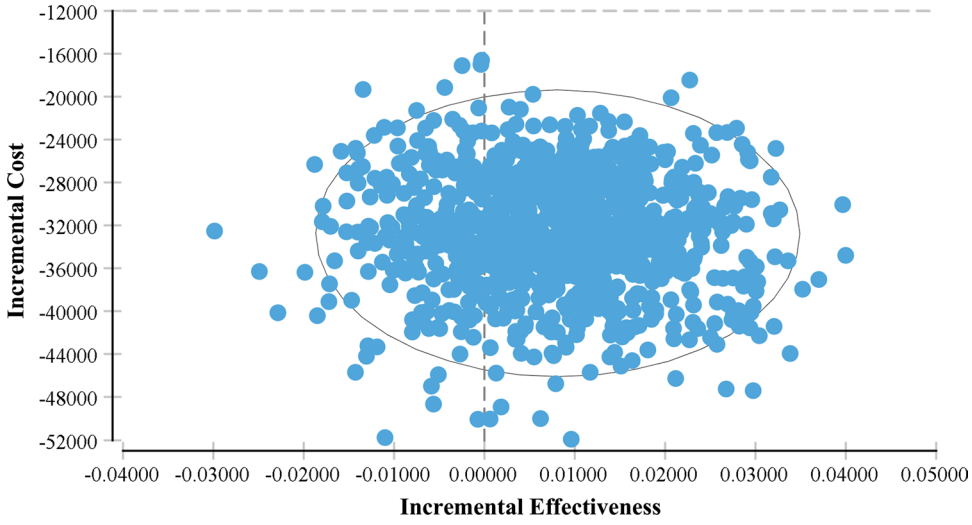

Fig. 3 Probabilistic analysis. Cost-effectiveness plane. The probability of cost-effectiveness from a societal perspective is 78%. *QALYS* quality-adjusted life years

Lower tumor grade ($P < 0.001$), higher levels of progesterone receptor (PR) positivity ($P < 0.001$), and low Ki67 expression ($P < 0.001$), were significantly associated with a greater possibility of changing from CHT to HT. Conversely, higher tumor grade ($P = 0.03$), lower levels of PR positivity ($P = 0.005$), and high Ki67 expression ($P < 0.001$), were associated with the likelihood of change from HT to CHT.

Patients` perception of GEAs in BC treatment decisions

A total of 59 patients from a single institution (Hospital Gregorio Marañón) participated in this study. Twenty-seven patients were highly educated (46%) and did not undergo CT (83%). Only 9 patients (15%) were aware of the existence of GEAs before they were offered by an oncologist. In 57 cases (97%) the test allowed patients to feel more confident with the treatment finally recommended.

Discussion

This is, in the best of our knowledge, the largest prospective study on the impact of GEAs on adjuvant decision making in ESBC in a homogeneous European patient population belonging to a single health care area and, in particular, the first to report on the clinical utility of two genomic tests, Oncotype DX® and MammaPrint®. Our study shows that treatment recommendations changed in 42.6% patients after GEAs results. The shift was predominantly from adjuvant CHT to HT alone (30.5%). In addition, the use of Onco*type* Dx and MammaPrint® compared with traditional prognostic factors is cost-saving from a national health system (by 13,920€ per patient) and from a societal perspective (by 32,793€ per patient). These savings occur with an improvement in QALYs.

The change rate of 42.6% from pre- to post-test recommendation is higher than the rate of 30% reported in previous studies [5–10]. A possible reason is that 56% of patients in our study were recommended CT prior testing. This could reflect the limited prognostic value of clinicopathological factors: inaccurate predictions of outcome may lead oncologists to be cautious and recommend adjuvant CT to most women with ESBC, making more patients eligible for the elimination of CT.

In our study oncologists seemed to be hesitant omitting CT in patients with intermediate RS determined by Oncotype DX®. HT alone was recommended to 23% of patients initially recommended CHT and 66% of patients with initial recommendation for HT were advised CHT post-test. A previous study conducted by Eiermann et al. [7] reported similar results: 60% of patients with initial recommendation for HT were advised CHT post-test. More importantly, 32% of patients with initial CHT recommendation were not advised to omit CT despite a low RS result. Thus, Oncotype Dx does not provide clear guidance on the optimal treatment of the intermediate risk group. The TAILORx prospective clinical trial was primarily designed to determine whether adjuvant CT produces a clinical benefit in patients with a midrange RS of 11–25.

Final results, published in 2018, show, that in women with a midrange RS, adjuvant HT and CHT have similar efficacy although some benefit of CT was found in some women 50 years of age or younger [28].

Few studies have explored the association between clinicopathological parameters and the possibility of change in treatment recommendation before and after Oncotype DX® or MammaPrint® testing. Tumor grade, Ki67 expression and levels of PR positivity were significantly associated with the likelihood of change from CHT to HT and from HT to CHT in this study. Albanell et al. [6] reported that positive PR status was significantly associated with a greater chance of changing to HT whereas intermediate–high tumor grade and high Ki67 expression were significantly associated with a greater chance of changing to CHT.

This is one of the few studies that has addressed patient perceptions of GEAs and thus provides novel insights into how and why patients value the test in their treatment decisions. Our results are consistent with literature demonstrating that women with BC want to participate in treatment decision making [29, 30].

Cost-effectiveness evaluations show that the use of GEAs are both cost- and life-saving in comparison with current clinical practice. Previous health economic analyses have shown that these tests are cost-effective, with clinical benefits being primarily driven by the sparing of CT [11]. A limitation of these analyses is that they are based on hypothesized use of adjuvant CT according to guideline recommendations. In the present study, we incorporate data from real patients as obtained from current clinical practice. Furthermore, our study has a number of strengths. BC and its treatment have a notable impact on personal and family life. The present study considers the impact of indirect costs associated with travel, lost work time and treatment costs associated with long-term side effects. Given that indirect costs account for more than 50% of the economic burden of cancer economic evaluations should include a societal perspective. Finally, it is worth mentioning, that cost-effectiveness analyses were performed by a health economics and research of outcomes consulting company and financed by the local health council in Madrid meaning that our results were not influenced by the interests of the pharmaceutical industry.

In interpreting these results several limitations must be considered. First, the numerical value of the RS provided by Oncotype DX® was not registered in the post-test questionnaires. Such information could have been valuable to better analyse final treatment recommendation in patients with an

intermediate RS after Oncotype DX® testing. Second, the utilities applied in the economic model were derived from the English-speaking literature and may not fully characterize the preferences of patients in Spain. Third, the present study did not include a long-term follow-up of patients tested, although it is planned in a future. The effect that treatment decision guided by GEAs may have on survival has therefore not been prospectively evaluated.

Conclusion

In summary, this study demonstrates that Oncotype DX® and MammaPrint® play a significant role in treatment management of patients with ESBC. It is associated with CT sparing in patients likely to derive little or no benefit from treatment. Results also illustrate that GEAs are cost-saving and highly cost-effective from a national health care system and a societal perspective.

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Compliance with ethical standards

Conflict of interest SPR received consultant/advisory honorarium from Janssen, Novartis, Roche, Pharma-Mar and Bayer; SLTC received consultant/advisory honorarium from Astrazeneca, Novartis, Roche, Pfizer, Gelgene, Pierre-Fabre, Eissai and Lilly; NMJ received consultant/advisory honorarium from Roche, Amgen, Pfizer, Gelgene and Eissai; IMR received consultant/advisory honorarium from BMS, MSD, Novartis, Roche, Pierre-Fabre, Bioncotech and Sanofi; CRT received funding from Hospital General Universitario Gregorio Marañón; DRR received funding from Hospital General Universitario Gregorio Marañón; JAGS received consultant/advisory honorarium from Novartis, Lilly, Celgene and Roche and Funding from AstraZeneca; FMA received consultant/advisory honorarium from Roche, Pfizer, Novartis and AstraZeneca; PZA received consultant/advisory honorarium from Roche and Novartis; MLA received consultant/advisory honorarium from Novartis, Celgene, Roche and Pfizer; EMCG received remuneration from Novartis, Lilly, Pfizer, Roche and consultant/advisory honorarium from Sama; LMS received consultant/advisory honorarium from Tesaro, Astra-Zeneca, Roche, Novartis and Celgene, and funding from Tesaro; SGA reports personal fees from Celgene, Roche, Pierre Fabre, Novartis and Astra Zeneca and non-financial support from Roche, outside the submitted work; MM received remuneration from Pfizer, Lilly; consultant/advisory honorarium from Roche, Novartis, Pfizer, Astrazeneca, Lilly, Glaxo, PharmaMar, Taiho; and funding from Roche and Novartis. MDMM, FLS, YIP, MAY, MJEG, JAGM, CJS, CBM, RCG, VVM declare that they have no conflict of interest.

Research involving human participants and/or animals This study has been approved by the Ethical Committee (Area 1 CEIm Hospital General Universitario Gregorio Marañón) and it has also been authorised by the local health council in Madrid and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent All eligible patients provided written informed consent prior to the inclusion in the study.

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