Genomic profile of breast cancer: Cost-effectiveness analysis from the Spanish NHS perspective

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Abstract

Background: Cost-effectiveness analysis of MammaPrint® in the diagnosis of early breast cancer.

Material and methods: Markov model assuming a cohort of 60-year-old women with breast cancer. Treatment costs and effects were assessed by comparing the 5-year, 10-year and lifetime risk of recurrence using Adjuvant!Online, MammaPrint® or OncotypeDX®.

Results: MammaPrint® showed a life expectancy of 23.55 years at lifetime. Life expectancy was lower for OncotypeDX® and Adjuvant! Online® vs. MammaPrint®, with associated long-term losses of 1.55 LY and 1.52 LY, respectively. At year five, the mean cost of OncotypeDX®, MammaPrint® and Adjuvant! Online® was €7,653, €6,380 and €4,744, respectively. MammaPrint® was dominant vs. OncotypeDX® at any time horizon and would be cost-effective from year 6 vs. Adjuvant! Online® (lifetime: €287 per QALY gained).

Conclusions: MammaPrint® was a dominant strategy over OncotypeDX® in predicting the risk of recurrence and was highly cost-effective vs. Adjuvant!Online®.

Keywords: cost-effectiveness, breast cancer, diagnosis, genotyping, MammaPrint®, OncotypeDX®.

1. Introduction

Breast cancer is the most common tumor type, with 93.6 new cases per 100,000 inhabitants in Spain [1]. Although improved screening and therapies have led to 5-year survival rates above 80% [2], it remains the leading cause of cancer death in Spanish women, with 26.93 deaths per 100,000 inhabitants [3].

Adjuvant chemotherapy increases survival but at the cost of significant toxicity, which has an impact on the quality of life (QoL) and the Spanish National Healthcare System (NHS) budget [4]. Therefore, chemotherapy should be limited to patients with a higher probability of tumor recurrence.

The decision of whether to administer adjuvant chemotherapy to patients with breast cancer is based on the estimated risk of recurrence [5]. For this decision, oncologists may use algorithms based on clinical-pathological criteria. Tumor recurrence can be predicted by various factors: lymph node involvement, tumor size, histology subtype and grade, vascular and lymphatic invasion, proliferation markers, hormone receptors and human epidermal growth factor receptor 2 (HER2) overexpression [4, 5].

Several prognostic tools have been designed as a response to the need for a quantitative approach to the diagnosis and rational individualization of treatment. Adjuvant! Online® is a computer based algorithm that aids health professionals make estimates of the risk of negative outcomes (cancer related mortality or relapse) without systemic adjuvant therapy, the reduction of these risks afforded by therapy, and the risks of side effects of the therapy. These estimates are based on individual patient information and the tumor characteristics (for example, patient age, tumor size, nodal involvement, histologic grade, etc.) [6, 201].

Recent advances in molecular biology have led to the development of gene expression microarrays that quantitatively assess the expression of multiple genes [7]. Differential gene expression has the potential to substantially refine cancer prognosis [8].

In patients suffering from breast cancer, gene expression profiling facilitates estimates of the risk of tumor recurrence in those patients with early stage disease [5]. The most widely used platforms are MammaPrint® and Oncotype DX® [7].

MammaPrint® evaluates the expression of 70 genes and classifies patients in low and high risk categories of recurrence [8]. Oncotype DX® evaluates the activity of 21 genes to determine the risk of recurrence and classifies patients in low, intermediate and high risk categories of recurrence [9]. The major drawback of Oncotype DX® is that an intermediate risk of recurrence makes therapeutic decisions more complex, as the benefit of chemotherapy in these patients is doubtful [5]. Nevertheless, both tools have been shown to be clinically useful in the prognosis of the risk of cancer recurrence [8, 9-16].

Accurate risk classification is required to identify patients at high risk of recurrence [17]. The proportion of patients classified as low and high risk may differ according to the tool used [17], implying variations in treatment decisions that may influence clinical and economic outcomes.

Direct breast cancer costs in Spain are estimated at € 517 million (€ 2013), of which chemotherapy is the second most-important cost item, accounting for 37% of the total [18]. Genetic profiling could lead to better resource allocation, reduce unnecessary chemotherapy costs, and increase QoL [17]. Therefore, comparison of risk recurrence classification methods is essential for decision making [19].

The objective of this study was to compare the cost-effectiveness of Adjuvant! Online® alone or followed by MammaPrint® or Oncotype DX® in the diagnosis of breast cancer in Spain.

2. Patients and methods

A pharmacoeconomic model was developed to compare the costs and effects of breast cancer treatment by identifying the risk of tumor recurrence using Adjuvant! Online® alone or followed by MammaPrint® or Oncotype DX® in a hypothetical group of 60-year-old women with lymph node-negative, estrogen receptor-positive, HER2-negative breast cancer.

The incremental cost-effectiveness ratio (ICER) was calculated using the formula:

$$(\text{Cost}_{\text{MammaPrint}^{®}} - \text{Cost}_{\text{Alternative}}) / (\text{Effectiveness}_{\text{MammaPrint}^{®}} - \text{Effectiveness}_{\text{Alternative}}),$$

in which $\text{Cost}_{\text{MammaPrint}^{®}}$ and $\text{Cost}_{\text{Alternative}}$ were the costs related to the use of MammaPrint® and the alternative option, respectively, and $\text{Effectiveness}_{\text{MammaPrint}^{®}}$ and $\text{Effectiveness}_{\text{Alternative}}$ were the clinical consequences in terms of life years (LY) or quality-adjusted life years (QALY) gained.

The analysis was performed for 5-year, 10-year and lifetime (40-years) horizons from the Spanish NHS perspective, considering only direct medical costs (€ 2013). Future costs and outcomes were discounted by 3% annually [20].

2.1. Classification in categories of risk recurrence

Patients were classified according to the tumor recurrence risk identified by Adjuvant! Online® and reclassified according to the predictions made by MammaPrint® and Oncotype DX® (figure 1).

According to a specifically-constituted panel of Spanish clinical experts, the probability of low and high risk of recurrence with Adjuvant! Online® was fixed at 50% for low risk and 50% for high risk. Reclassification in each risk category was based on studies that evaluated the sensitivity and specificity of risk prediction using MammaPrint® [8, 10-12] or Oncotype DX® [13-16] with respect to the risks predicted by Adjuvant! Online® (table 1). As Oncotype DX® reclassified patients in high, intermediate and low-risk categories, the MammaPrint® high-risk category was assumed to be equal to the weighted merging of the intermediate and high-risk categories in Oncotype DX® [9] (table 1).

2.2. Model description

Depending on the risk category identified and according to expert opinion, patients were prescribed hormone therapy alone or in combination with adjuvant chemotherapy (table 2).

A 6-month cycle Markov model was constructed in TreeAge Pro 2011 [202] by defining three health states to simulate patient evolution (figure 1). All patients were entered in the model in the ”free of recurrence” state and remained there if they responded to treatment, or advanced to the “recurrence” or “death” state if they did not. Patients were at risk of death in any of the states.

A literature search identified the risk of tumor recurrence and breast cancer-related death according to the risk recurrence category and therapy (table 3). The risk of recurrence for the group identified as high risk by Adjuvant! Online® was based on published results [21]. For the low-risk group, calculations were based on results using an Adjuvant! Online® simulation for 60-year-old women with node-negative, estrogen receptor-positive breast cancer not receiving systemic adjuvant therapy [6] (table 3).

The probability of recurrence after MammaPrint® was based on the study by Buyse et al. [8]. As this study did not assess the benefits of adjuvant therapy, the probabilities of recurrence according to therapeutic alternative were estimated from Adjuvant! Online® simulations as the relative risk of recurrence with hormone therapy vs. no treatment and with hormone therapy + chemotherapy vs. no treatment [6, 8] (table 3). Conservatively, the probabilities of the risk of recurrence predicted by Oncotype DX® were assumed to be the same as MammaPrint®.

The model considered cancer-related mortality [21] (table 3), death due to treatment toxicity of 0.4% (0%-1%) [22] and the probability of death in Spain for the overall population [3].

2.3. Utility

Health outcomes were expressed in terms of QALY, which were defined as the survival rate in a cycle times the health utility associated with a given health state. Health utilities are cardinal values that reflect societal preferences for different health outcomes [23]. A utility value of 1 represents an ideal state of perfect health, whilst 0 represents death.

In order to describe the quality of life of patients diagnosed with breast cancer, a utility value of 0.8 was considered for the patients in the "free of recurrence" state [24] and a utility value of 0.5 for the patients in the "recurrence" state [25]. Patients receiving chemotherapy were assigned a utility of 0.5 [24].

2.4. Resource use and costs

The cost of the genetic testing devices corresponds to the actual Spanish market price.

The use of resources needed to estimate the cost of chemotherapy was obtained using an ad-hoc questionnaire and consensus sessions with a panel of experts (authors of the manuscript).

For each state, visits to specialist physicians (oncologists, gynecologists or radiotherapists), diagnostic tests (complete blood count, tumor markers, abdominal Echo, abdomen/thorax CT, bone gammagraphy, ventriculography or mammography) and drug therapy (hormone therapy, biological therapy, epoetin, bisphosphonates and others) were considered. These resources, together with the resources used in the treatment of adverse events that occurred during chemotherapy, were used to estimate the total cost of chemotherapy (table 4).

The most common chemotherapy regimens in Spain were identified by the panel of experts. It was assumed that 20% of patients received an FAC/AC/FEC regimen (6 FAC cycles with 5-FU 500mg/m2 + doxorubicin 50mg/m2 + cyclophosphamide 500mg/m2, 4 AC cycles with docetaxel 60mg/m2 + cyclophosphamide 600mg/m2 and 6 FEC cycles with 5-FU 500mg/m2+epirubicin 60mg/m2 + cyclophosphamide 500mg/m2. 40% of the patients received TC (docetaxel 75 mg/m2 + cyclophosphamide 600 mg/m2) and the remaining 40% of patients received AC+Paclitaxel/TAC (AC+Paclitaxel with

doxorubicin 60mg/m24 cycles + cyclophosphamide 600mg/m2 4 cycles + paclitaxel 80mg/m2 12 cycles and 6 TAC cycles with docetaxel 75 mg/m2 + doxorubicin 50mg/m2+ cyclophosphamide 500 mg/m2 + filgastrim 0.005 mg/m2). The drug cost was calculated for an average Spanish patient with a body surface of 1.7m^2 and a weight of 68 Kg.

In addition to chemotherapy costs, drug costs related to the management of adverse events were also considered by estimating the incidence of adverse events for each chemotherapy regimen using studies that assessed the efficacy and safety of the most common chemotherapy regimens used to treat women diagnosed with HER2-positive breast cancer [26-35] and the estimated cost of treatment of each of these adverse events [36]. All pharmacological costs used to calculate the chemotherapy cost were extracted from the Spanish database of drugs using ex-factory prices [37]. All other costs were extracted from eSalud, a Spanish database of costs [36]. All costs are expressed in 2013 Euros (table 4). Costs are expressed as an average of the total costs incurred in the treatment of the simulated cohort.

Furthermore, the follow-up costs of patients without metastasis ("Free of recurrence") and the costs of patients who suffered metastases ("Recurrence") were also considered in the analysis (table 4) [38].

2.5. Sensitivity analysis

A deterministic sensitivity analysis was performed by separately varying those model parameters which were considered to be uncertain. High and low values were determined by consensus with the panel of experts. Furthermore, a tornado diagram was used to determine which of the parameters had more impact on the final results (ICER).

The analysis was performed for the following parameters:

- Chemotherapy cost (High: € 5,428; Low: € 960).
- OncotypeDX® (High: € 3,200; Low: € 0).
- Metastatic cancer cost (High: € 7,311; Low: € 5,404).
- Age (High: 69; Low: 50).
- Classification with Adjuvant! Online® – Low: The proportion of patients that are classified as low risk of recurrence with Adjuvant! Online® (High: 60%; Low: 40%).
- Probability of Chemotherapy- Adjuvant! Online® High: The proportion of patients receiving chemotherapy when the risk of recurrence was identified as high after the Adjuvant! Online® assessment (High: 100%; Low: 90%).
- Reclassification: Adjuvant! Online® Low/ Oncotype DX® - High: The proportion of patients classified as low risk of recurrence with Adjuvant! Online® are reclassified as high risk of recurrence with Oncotype DX® (High: 44%; Low: 35%).
- Reclassification: Adjuvant! Online® High/ Oncotype DX® - Low: The proportion of patients classified as High risk of recurrence with Adjuvant! Online® are reclassified as Low recurrence risk with Oncotype DX® (High: 30%; Low: 20%).
- Probability of Chemotherapy- Low: The proportion of patients receiving chemotherapy when the risk of recurrence was identified as low (High: 5%; Low: 9%).

In addition, the effect of the uncertainty of any of the parameters during the patients' lifetime was evaluated using multivariate sensitivity analysis with a second-order Monte-Carlo simulation. The cost-effectiveness analysis was simulated 10,000 times for each comparison [39] to validate the robustness of the results. Gamma distributions were applied for the costs, 1-gamma distributions were applied for the utilities, a beta distribution was applied for probabilities and a triangular distribution was applied for the classification and for the parameters provided by the panel of experts. Once the distributions were fixed, parameters based on the primary data collected were estimated [40].

3. Results

3.1. Clinical benefits

MammaPrint® showed a life expectancy of 4.40, 8.91 and 23.55 years at 5 years, 10 years and lifetime, respectively (table 5). Life expectancy was lower for Adjuvant! Online® alone and followed by Oncotype DX® vs. MammaPrint®, with associated long-term losses of 1.55 LY and 1.52 LY, respectively (table 5), and 1.41 and 1.32 QALYs lost, respectively, and MammaPrint® remained the optimal choice. MammaPrint® reduced 25.3% of chemotherapy referrals with respect to Adjuvant! Online® alone and 19.7% with respect to Oncotype DX®.

3.2. Economic benefits

At year five, the mean cost of using Oncotype DX®, MammaPrint® and Adjuvant! Online® was € 7,653, € 6,380 and € 4,744, respectively. MammaPrint® was € 1,273 and € 2,909 more costly than Oncotype DX® and Adjuvant! Online® respectively (table 5).

The difference in cost between MammaPrint® and Adjuvant! Online® and Oncotype DX® diminished as the assessment time horizon increased.

3.2.1. MammaPrint® vs. Adjuvant! Online®

At 10 years, the reduction in chemotherapy requirements resulted in lower chemotherapy costs (€ 871 vs. € 1,580) and lower event management costs (€ 5,498 and € 6,310, respectively) for MammaPrint® vs. Adjuvant Online®, although this did not compensate for the cost of acquisition of MammaPrint® (table 6). Nevertheless, the difference in costs was reduced to € 1,149 from € 2,909 in the first five years of the analysis (Table 2). Furthermore, at the lifetime horizon, the cost difference between the total treatment of patients tested with MammaPrint® was only € 378 greater than that of patients tested using only Adjuvant! Online® (Table 2). Therefore, the better prognosis almost compensated for the cost of acquisition of MammaPrint®.

3.2.2. MammaPrint® vs. Oncotype DX®

The mean additional cost of Oncotype DX® compared to MammaPrint® was € 2,909 at year 5, € 3,164 at year 10 and € 4,058 at lifetime (table 5). At 10 years, Oncotype DX® presented higher cumulative costs than the alternative tools at any horizon due to higher chemotherapy costs, worse prognosis rates and the higher cost of the device (table 6).

3.3. Cost-effectiveness analysis

3.3.1. MammaPrint® vs. Adjuvant! Online®

At 5 years, MammaPrint® showed ICERs of € 43,912/QALY and € 62,794/LY gained vs. Adjuvant! Online® (table 5). Considering the ICER threshold for Spain (€ 30,000

per LY and QALY gained [30]), MammaPrint® would be cost-effective after 6 years in terms of QALYs and 7 years in terms of LY vs. Adjuvant! Online®. The ICERs of MammaPrint® vs. Adjuvant! Online® were € 6,169/QALY gained at 10 years and € 287/QALY gained at lifetime (table 5-6).

3.3.2. MammaPrint® vs. Oncotype DX®

Due to its greater efficacy and lower associated cost, MammaPrint® resulted a dominant testing alternative with respect to Oncotype DX® at any time horizon.

3.4. Sensitivity analysis

3.4.1. MammaPrint® vs. Adjuvant! Online®

Deterministic sensitivity analysis showed that when comparing MammaPrint® with Adjuvant! Online®, chemotherapy, the costs of metastatic cancer and the proportion of patients initially classified as high or low risk of recurrence by Adjuvant! Online® were the key drivers of the results (figure 2).

A reduction in the proportion of low-risk patients using Adjuvant! Online® equated to the QALYs obtained by Oncotype DX® and Adjuvant! Online®, albeit with an increase in costs. This reduction resulted in lower ICERs than those observed in the base case. An increase in the proportion of low-risk patients using Adjuvant! Online® would increase the ICER for MammaPrint® vs. Adjuvant! Online® to almost € 10,000/QALY gained, which is still below the acceptable efficiency threshold for Spain [30]. Increasing the age at baseline resulted in lower life expectancy and worse QoL, but MammaPrint® remained cost-effective.

3.4.2. MammaPrint® vs. Oncotype DX®

The results of the comparison of MammaPrint® with Oncotype DX® (Figure 2) suggest that Mammaprint® remains dominant up to a price of Oncotype DX® of € 1,150, and was cost-effective even when Oncotype DX® was considered to have no cost (€ 0) (figure 2).

Modification of chemotherapy costs, and reclassification of Oncotype DX® risks into high and low did not change the results, with MammaPrint® remaining dominant compared to Oncotype DX® (figure 2).

Probabilistic sensitivity analysis confirmed that, in the long-term, MammaPrint® is cost-effective vs. Adjuvant! Online® and dominant vs. Oncotype DX® (figure 3). MammaPrint® would be a cost-effective intervention for the Spanish NHS and would be so up to a willingness-to-pay threshold of < € 275/QALY gained (figure 4).

4. Discussion

Drug costs are the key drivers of cancer-related costs and are expected to increase in coming years with the approval of new treatments [18]. Eliminating all unnecessary drug treatments would reduce the economic impact of cancer on the NHS and improve efficiency. Gene expression profiles, such as MammaPrint® and Oncotype DX®, could help identifying high risk of recurrence early stage breast cancer patients that would benefit from adjuvant chemotherapy [17]. In addition, they represent a meaningful advance in the process of involving patients in the treatment decision making process [6].

This is the first cost-effectiveness analysis to compare MammaPrint® and Oncotype DX® in Spain and our results are similar to those of other studies [19, 31-34]. A U.S study, carried out in a similar population and using a comparable methodology and assumptions, recommended replacing Oncotype DX® with MammaPrint® as it was more cost-effective [19], supporting our results. Moreover, MammaPrint® was found to be cost-effective in the US setting compared with Adjuvant! Online® in women with early-stage breast cancer [31]. In the Netherlands, MammaPrint® and Oncotype DX® were cost-effective vs. Adjuvant! Online® using QALYs and LYs, respectively, to measure effectiveness [32, 33]. Although these models differed from ours and from that used by Yang et al. [11] with respect to reclassification after Adjuvant! Online® [31-34], they still indicate the differential benefits of MammaPrint®. Furthermore, a prospective cost-effectiveness analysis showed that MammaPrint® was dominant vs. Adjuvant! Online® (less costly and more effective) [34].

Our results suggest MammaPrint® could reduce the proportion of patients receiving chemotherapy compared with Oncotype DX® and Adjuvant! Online®, thereby reducing the cost per patient and improving the allocation of healthcare resources. Moreover, MammaPrint® would produce greater clinical benefits in terms of LYs and QALYs vs. Oncotype DX® and Adjuvant! Online® for all time horizons considered.

Nevertheless, this analysis has several limitations that should be taken into account when interpreting the results. MammaPrint® has been cleared by the U.S. Food and Drug Administration and genetic profiling is included in clinical guidelines, although the largest clinical trials testing the predictive power of MammaPrint® and Oncotype DX® are still ongoing [35, 41]. The lack of reliable efficacy results is a limitation of our study, as it was for other analyses [19, 31-34], and therefore more evidence is required [17]. To overcome this limitation, efficacy data were analyzed conservatively, with the

eventual superiority of MammaPrint® in terms of efficacy being underestimated. Moreover, when information was not available from clinical trials or published reports, conservative assumptions were made and validated by a panel of Spanish clinical experts. We assumed that the risk predictions using Oncotype DX® were as reliable as those provided by MammaPrint® even though, in the absence of adjuvant systemic treatment, the 10-year recurrence-free survival with Oncotype DX® in the low and intermediate groups is lower than that in patients treated with tamoxifen for 5 years [42]. This was a conservative assumption that allowed assessment of the effect of identifying the risk of recurrence of genetic testing prior to treatment.

We restricted the model to the subgroup where Oncotype DX® has been validated, with all patients being expected to receive tamoxifen for 5 years, a necessary condition for Oncotype DX® [9] but not for MammaPrint®. Studies of MammaPrint® [7] and Oncotype DX® [9, 13] had different designs with respect to the measurement of risk recurrence: Paik et al. [9, 13] evaluated differences between patients treated with hormone in monotherapy or in combination with chemotherapy, whereas Buyse et al. [8] evaluated patients without adjuvant systemic treatment. As the OncotypeDX® risk is conditioned to 5 years of tamoxifen, the risk in patients who discontinue treatment before completion (15-50% of cases in clinical practice) is unclear [39, 40, 43-45]. Conversely, MammaPrint® identifies tumor risk, as it is not conditioned by adjuvant systemic treatment [8, 46, 47]. Consequently, it is reasonable to assume that each method provides different classifications for the same patient, as shown by other studies [19]. In addition, OncotypeDX® can provide uncertain efficacy responses for the intermediate group [5, 7, 33].

However, as previously mentioned, the limitations and assumptions of the study have been validated by clinical experts and extensively evaluated in the various sensitivity analyses, which confirmed the robustness of the results.

In conclusion, the use of MammaPrint® as a prognostic tool to predict the risk of recurrence in patients with early breast cancer was a dominant strategy over Oncotype DX® and was highly cost-effective with respect to Adjuvant! Online®.

5. Conclusion

The results of the analysis recommend MammaPrint® as the genetic test of choice from the health economics point of view, as it was a dominant strategy over Oncotype DX® in predicting the risk of recurrence and was highly cost-effective vs. Adjuvant! Online®.

6. Five-year view

The need to avoid over- and under treatment in the curative adjuvant setting has motivated the search for efficient prognostic and predictive markers in early breast cancer over the last two decades. Multi-gene assays have provided a new approach not only to breast cancer subtyping but also to prognostic and predictive tumor classification.

The use of multi-gene assays in early-stage breast cancer has improved decision-making in adjuvant chemotherapy. The results of the ongoing prospective trials are eagerly awaited and will show whether these tests should be the standard of care.

Gene-expression assays and technology are constantly evolving and, in the future, structured tools that integrate clinical and genomic features, will probably become available. The clinical validity and reliability of innovations for patient management must be addressed rapidly. Technical ease and price will be crucial when considering the general implementation of these tests in clinical practice.

Specifically, reports suggest that MammaPrint® is likely to be cost-effective in patients with ER+ early-stage breast cancer. Future studies investigating head-to-head comparisons of gene-expression assays would yield valuable insights into how these tests influence adjuvant therapy decision making, and would provide valuable data for future economic evaluations on the relative merits of these tests in clinical practice.

Combining one or more gene-expression classifiers into a single model together with traditional clinico-pathological parameters that still retain significant prognostic information would provide a greater level of understanding of tumor biology that could improve the daily management of breast cancer patients.

It is to be hoped that the judicious use of these tests will allow continued improvements in the management of patients with early stage breast cancer. Cost-effectiveness issues will become even more important, given the expected rises in treatment costs and their impact on patients' quality of life and the NHS budget. Further studies on the economics of multi-gene assays will be crucial helping to guide treatment for patients living with this serious disease.

7. Key Issues:

- Breast cancer is the most common tumor type in Spain and the leading cause of cancer death in Spanish women.

- Adjuvant chemotherapy increases survival but at the cost of significant toxicity, which has an impact on quality of life (QoL) and the Spanish National Healthcare System (NHS) budget. Therefore, chemotherapy should be limited to patients with a higher probability of recurrence.

- Gene expression profiles help identify patients with a higher probability of recurrence and could lead to better resource allocation, reduce unnecessary chemotherapy costs and increase QoL.

- Gene expression profiles are an essential tool for public health decision-making in early stage breast cancer.

- MammaPrint® is a dominant strategy over OncotypeDX® in predicting the risk of recurrence and avoiding chemotherapy overtreatmentMammaPrint® is a highly cost-effective strategy vs. Adjuvant! Online®.

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Figure 1. Structure of the Markov model used to simulate the disease course

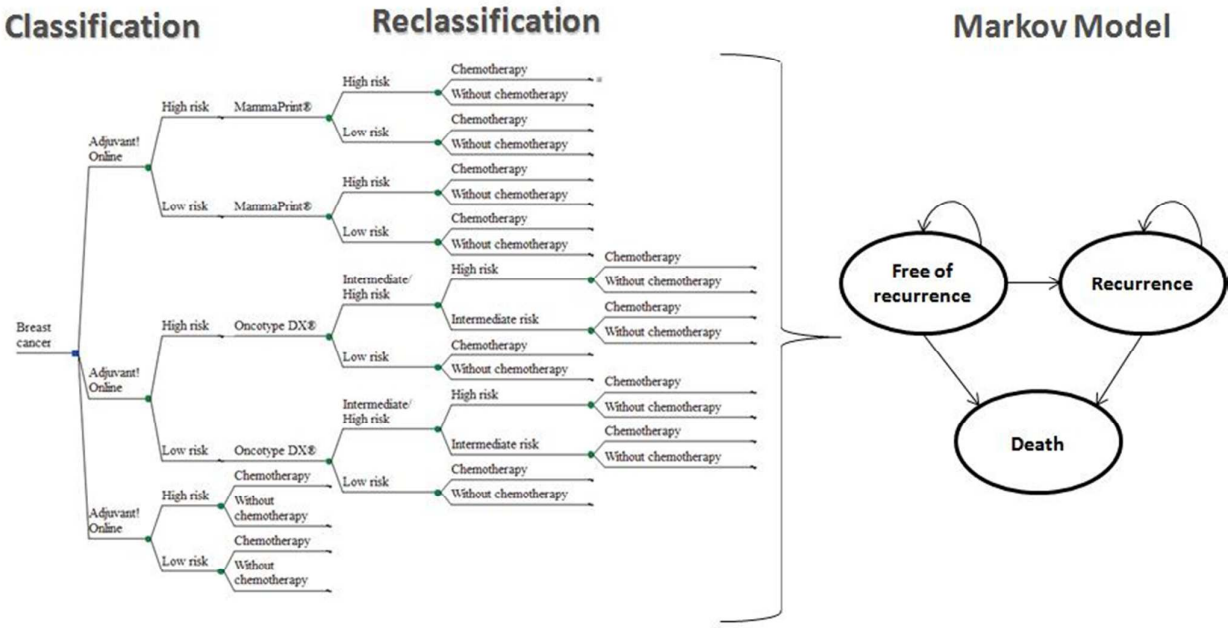
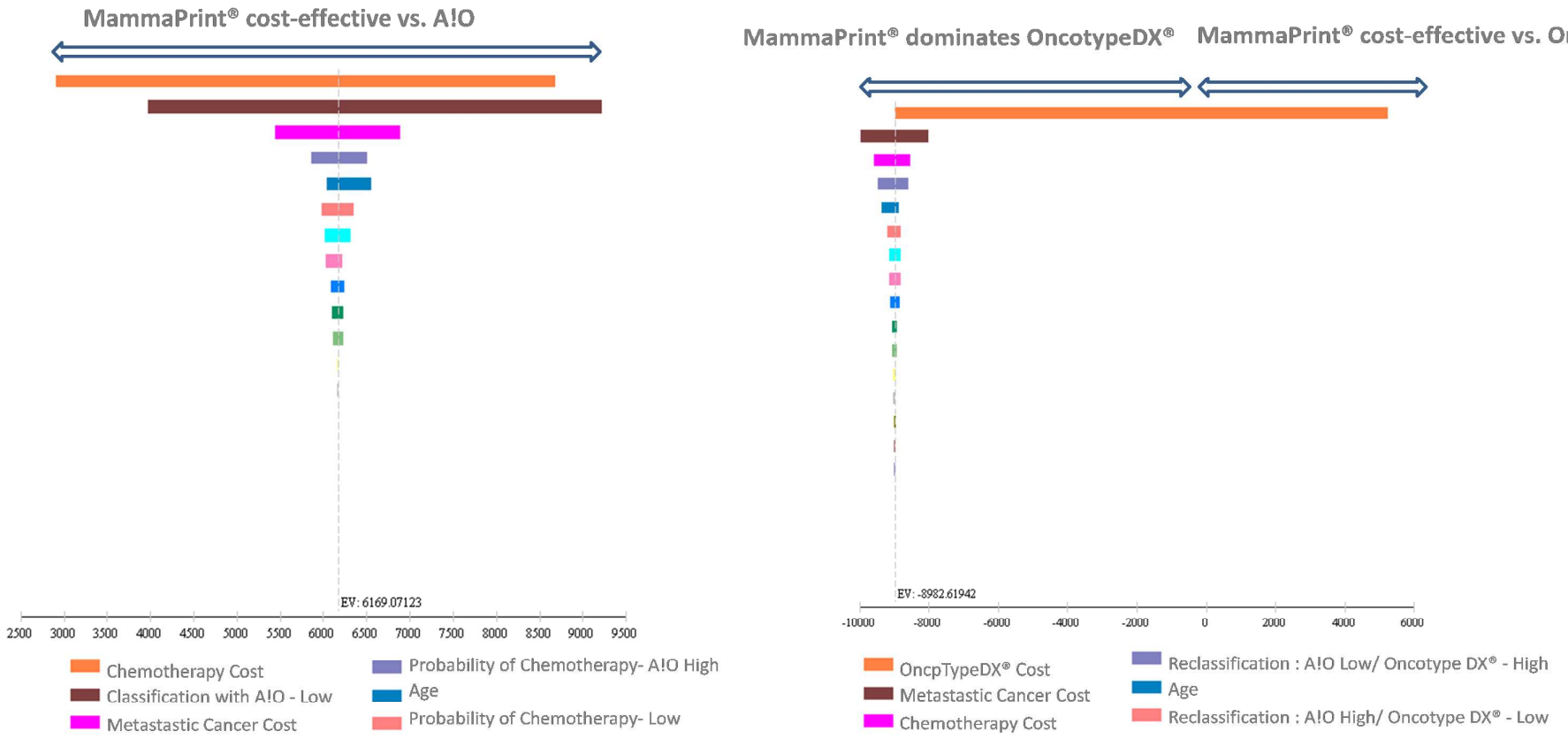
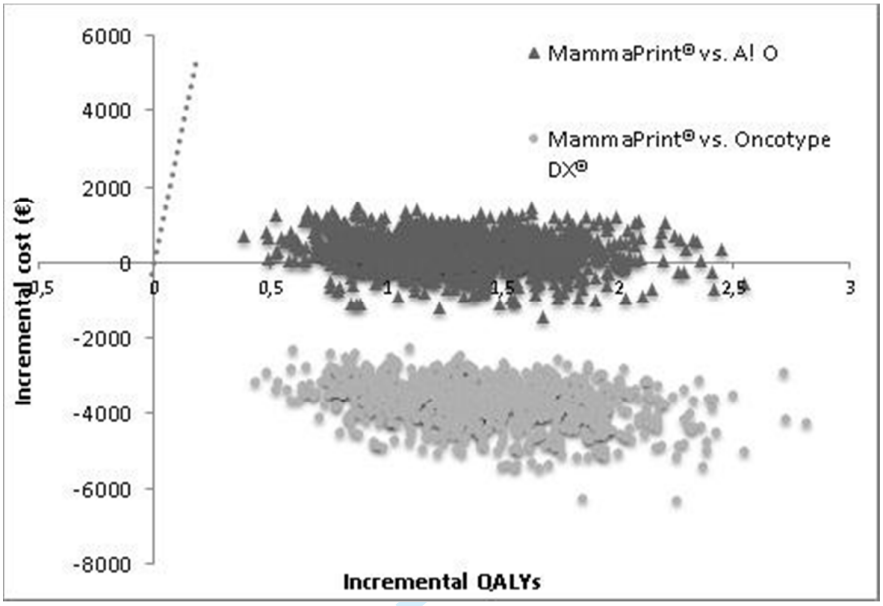


Figure 2. Univariate Deterministic Analysis (ICER)



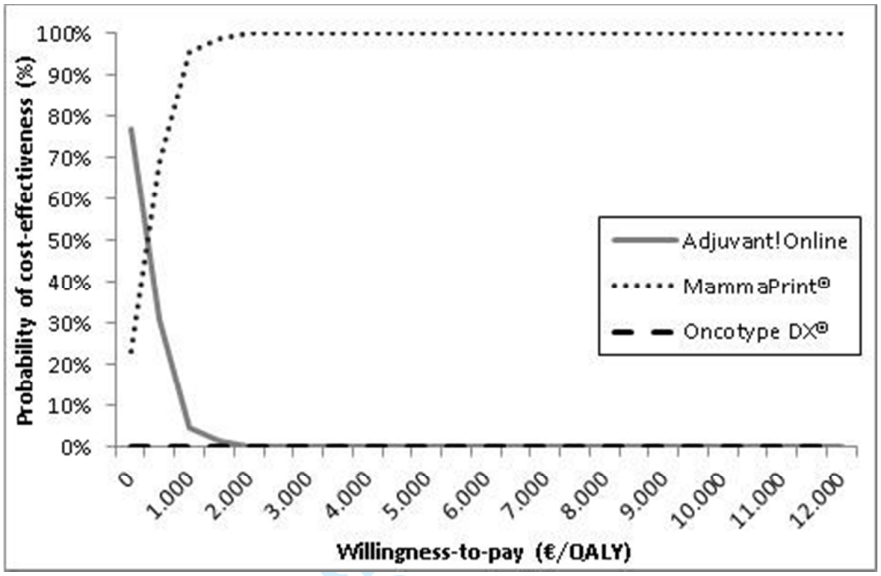
A!O: Adjuvant! Online

Figure 3. Probabilistic Sensitivity Analysis



A!O: Adjuvant Online; QALY: quality-adjusted life year

Figure 4. Cost-Effectiveness Acceptability Curve



QALY: quality-adjusted life year

Table 1. Risk recurrence reclassification with MammaPrint® and OncotypeDX®

Genetic test	A!O	
	Low-risk	**High-Risk**
MammaPrint® (% coincidence)	78.7% (75.5-81.7%)	61.3% (58.1-64.5%)
OncotypeDX® (% coincidence)	59.0% (55.2-62.7%)	33.56% (29.2-37.9%)
Intermediate-risk OncotypeDX®	30.6% (28.5-32.7%)	26.7% (23.1-30.2%)

A!O: Adjuvant Online

Table 2. Probability of treatment with chemotherapy depending on the recurrence risk identified

Test Risk Category		A!O	
		High Risk	**Low-risk**
Adjuvant!Online		90-100%	15-20%
OncotypeDX®	High	95-100%	95-100%
	Intermediate	60-80%	20-40%
	Low	0-5%	0-5%
MammaPrint®	High	95-100%	95-100%
	Low	0-5%	0-5%

A!O: Adjuvant Online

Table 3. 10-year recurrence risk and mortality

Test	Risk	Treatment	RECURRENCE A!O LOW	RECURRENCE A!O HIGH	CANCER-RELATED MORTALITY A!O LOW	CANCER-RELATED MORTALITY A!O HIGH
Adjuvant!Online*		No CHEMO	10.3%	39.8%	7.1%	27.6%
		CHEMO	9.3%	29.6%	6.8%	21.5%
MammaPrint®**	**LOW**	No CHEMO	8.60%	11.90%	6.00%	8.30%
		CHEMO	7.80%	10.80%	5.60%	7.80%
	HIGH	No CHEMO	17.00%	25.30%	11.80%	17.50%
		CHEMO	14.90%	22.20%	10.80%	16.10%
OncotypeDX®**	**LOW**	No CHEMO	8.60%	11.90%	6.00%	8.30%
		CHEMO	7.80%	10.80%	5.60%	7.80%
	INTERMED.	No CHEMO	16.10%	18.10%	11.20%	12.60%
		CHEMO	14.10%	15.90%	10.30%	11.50%
	HIGH	No CHEMO	17.70%	32.20%	12.30%	22.30%
		CHEMO	15.50%	28.30%	11.30%	20.50%

A!O: Adjuvant Online; CHEMO: Chemotherapy; *Based on a 60-year-old patient with node-negative. ER-positive breast cancer not receiving adjuvant therapy with a recurrence risk of 16.1%. **Patients in the high, intermediate and low risk categories of MammaPrint® and OncotypeDX®, are not the same as initially classified by A!O high and low.

Table 4. Main costs included in the model (€ 2013)

	COST (€)
MammaPrint®	€ 2,675 [Spanish Market Price]
Oncotype DX®	€ 3,200 [Spanish Market Price]
Chemotherapy*	€ 2,825 (€ 960;€ 5,248) [23, expert opinion]
Free of recurrence (1st year)	€ 645 (€ 549;€ 742) [24, expert opinion]
Free of recurrence (2nd year)	€ 597 (€ 508;€ 687) [24, expert opinion]
Free of recurrence (3rd+ year)	€ 258 (€ 219;€ 297) [24, expert opinion]
Recurrence (per year)	€ 6,358 (€ 5,404;€ 7,311) [24, expert opinion]

*Including drug costs, the cost of adverse effects (AE) estimated from the incidence [26-28] and unit costs [24-25] of AEs and administration costs [25].

Table 5. Cost-effectiveness analysis.

	AVERAGE COST (€)	LY	QALY
Year 5			
Adjuvant!Online	€ 4,744	4.374	3.277
OncotypeDX®	€ 7,653	4.370	3.260
MammaPrint®	€ 6,380	4.400	3.314
ICER MammaPrint® vs. Adjuvant!Online		€ 62,794 /LY	€ 43,912 /QALY
ICER MammaPrint® vs. OncotypeDX®		Dominant	Dominant
Year 10			
Adjuvant!Online	€ 7,890	8.730	6.662
OncotypeDX®	€ 11,054	8.715	6.624
MammaPrint®	€ 9,039	8.910	6.849
ICER MammaPrint® vs. Adjuvant!Online		€ 6,387/LY	€ 6,169 /QALY
ICER MammaPrint® vs. OncotypeDX®		Dominant	Dominant
Lifetime			
Adjuvant!Online	€ 16,611	22.029	17.041
OncotypeDX®	€ 20,669	21.997	16.945
MammaPrint®	€ 16,989	23.551	18.357
ICER MammaPrint® vs. Adjuvant!Online		€ 248 /LY	€ 287 /QALY
ICER MammaPrint® vs. OncotypeDX®		Dominant	Dominant

ICER: Incremental cost-effectiveness ratio; LY: Life year; QALY: Quality-adjusted life year.

Table 6. Total treatment cost at 10 years

Type of cost	MammaPrint®	OncotypeDX®	A!O
Events management costs	€ 5,498	€ 6,834	€ 6,310
Genetic test costs*	€ 2,670	€ 3,193	€ -
Chemotherapy Costs**	€ 871	€ 1,027	€ 1,580
Total Costs	**€ 9,039**	**€ 11,054**	**€ 7,890**

A!O: Adjuvant Online; *Cost considering that in the chemotherapy arm of the model patients have an initial probability of death, therefore no cost associated to MammaPrint® and OncotypeDX® in those cases; **Including drug costs, the cost of adverse effects (AE) estimated from the incidence [26-28] and unit costs [24-25] of AEs and administration costs [25].