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ORIGINAL REPORT

Cost Effectiveness of Molecular Profiling for Adjuvant Decision Making in Patients With Node-Negative Breast Cancer

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
To conduct an economic evaluation of the 70-gene signature used to guide adjuvant chemotherapy decision making both in patients with node-negative breast cancer (NNBC) and in the subgroup of estrogen receptor (ER) –positive patients.

Patients and Methods
We used a mixed approach combining patient-level data from a multicenter validation study of the 70-gene signature (untreated patients) and secondary sources for chemotherapy efficacy, unit costs, and utility values. Three strategies on which to base the decision to administer adjuvant chemotherapy were compared: the 70-gene signature, Adjuvant! Online, and chemotherapy in all patients. In the base-case analysis, costs from the French National Insurance Scheme, life-years (LYs), and quality-adjusted life-years (QALYs) were computed for the three strategies over a 10-year period. Cost-effectiveness acceptability curves using the net monetary benefit were computed, combining bootstrap and probabilistic sensitivity analyses.

Results
The mean differences in LYs and QALYs were similar between the three strategies. The 70-gene signature strategy was associated with a higher cost, with a mean difference of €2,037 (range, €1,472 to €2,515) compared with Adjuvant! Online and of €657 (95% CI, −€642 to €3,130) compared with systematic chemotherapy. For a €50,000 per QALY willingness-to-pay threshold, the probability of being the most cost-effective strategy was 92% (76% in ER-positive patients) for the Adjuvant! Online strategy, 6% (4% in ER-positive patients) for the systematic chemotherapy strategy, and 2% (20% in ER-positive patients) for the 70-gene strategy.

Conclusion
Optimizing adjuvant chemotherapy decision making based on the 70-gene signature is unlikely to be cost effective in patients with NNBC.

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INTRODUCTION

Node-negative breast cancer (NNBC), which accounts for 70% to 80% of the cases detected in screening programs,[1-3] has a favorable outcome, with a 30% to 32% breast cancer mortality rate without chemotherapy.[4] Because such treatment generates serious adverse effects, worsens quality of life, and generates costs,[5] a major current clinical objective is to restrict its indications to patients at high risk of recurrence.[6]

Research has focused on prognostic information to guide decision making regarding adjuvant chemotherapy. Several tools have been developed to predict individual risk of recurrence aimed at selecting the optimal adjuvant therapy. Prognostic models[7] using patient- and tumor-related factors seemed to fall short of accurately predicting the risk of recurrence on an individual basis.[8] Thus, tumor biomarkers and genomic signatures, aimed at more accurately predicting prognosis, have been investigated. The added value of these genomic tests beyond standard clinical and pathologic prognostic factors is still under investigation and fueling debate.[9-11]

Unlike prognostic models such as Adjuvant! Online, which are available free of charge, genomic tests are costly. If the clinical usefulness of genomic tests were demonstrated,[12] payers would be faced with the decision of whether to reimburse for the use of these new health technologies in routine practice. Robust economic evaluations are therefore required

to inform these reimbursement decisions. Several economic evaluations of MammaPrint and OncotypeDX in NNBC have been published.[13-22] Most of these studies seem limited because of the quality of the available evidence and uncertainty surrounding health outcomes, which were rarely correctly reported.[12,23] Moreover, taxane-based regimens were mainly responsible for the high cost of chemotherapy.[24] However, since 2011, docetaxel has been available as a generic medicine in the United States and in Europe. Thus, the conclusions of some previous cost-effectiveness studies are no longer valid. For all these reasons, we decided to conduct an independent and updated economic evaluation of genomic test–driven chemotherapy in patients with NNBC in the French context. Our objective was to assess the cost effectiveness of the 70-gene signature (MammaPrint) to guide adjuvant chemotherapy decision making both in patients with NNBC and in the subgroup of estrogen receptor (ER) –positive patients.

PATIENTS AND METHODS

Study Design and Comparators

To assess the cost effectiveness of MammaPrint, we used a mixed approach described elsewhere,[25] combining patient-level clinical data (trial-based approach) from the TRANSBIG consortium validation study on MammaPrint[26] performed in untreated patients and secondary sources for chemotherapy efficacy, unit costs, and utility values (model-based approach). The checklist items from the Consolidated Health Economic Evaluation Reporting Standards[27] were used to report this cost-effectiveness study.

In France, as elsewhere in the world, there are hardly any data available to reliably describe the clinical practices of chemotherapy prescription in patients with NNBC. We considered two comparators. First, a strategy based on Adjuvant! Online, using clinical and pathologic predictors, was chosen to represent the current practice of oncologists. However, it is difficult to know whether the current practices are fully consistent with Adjuvant! Online. We therefore decided to consider a strategy with systematic chemotherapy in all patients as an alternative comparator, because most patients with NNBC are likely to be treated, especially if they are young.

Clinical Database

We used the database (patient-level data) from the TRANSBIG consortium validation study[26] on MammaPrint comprising 307 patients who did not receive any systemic adjuvant therapy. Only patients age < 61 years at diagnosis with a tumor size < 5 cm were eligible. Most patients had ER-positive disease (69%) and a grade 2 or 3 tumor (41%). In this clinical database, a binary high- or low-risk classification according to Adjuvant! Online or MammaPrint, respectively, was available for each patient in addition to survival data. In that series, 77 metastases and 82 deaths were observed, with a median follow-up of 13.6 years.

Key Assumptions

In the base-case analysis, we compared three strategies (MammaPrint, Adjuvant! Online, and systematic chemotherapy in all patients) to decide whether to administer adjuvant chemotherapy in 307 patients, with a 10-year time horizon. With the first two strategies, only women classified as being at high risk for recurrence were assumed to receive chemotherapy. In the systematic chemotherapy strategy, all patients were assumed to receive chemotherapy irrespective of their estimated risk of recurrence. We chose to focus on distant recurrence as opposed to any recurrence, because metastasis-free survival was the clinical end point used to define the Mammaprint 70-gene signature.[28] The absolute risk reduction afforded by adjuvant chemotherapy was assumed to be the same for both distant metastasis and overall deaths. We used a hazard ratio (HR) of 0.67 (95% CI, 0.51 to 0.88), which corresponds to the breast cancer mortality HR associated with a third-generation anthracycline-taxane–based regimen derived from the Early Breast Cancer Trialists' Collaborative Group meta-analyses of randomized controlled trials[4,29] (Appendix, online only). To model the efficacy of a strategy (chemotherapy exclusively in high-risk patients), we used the method developed by Stewart et al[30] (Appendix, online only), which consists of applying the Oxford meta-analysis HR to the survival functions in high-risk patients in our database (untreated patients). We assumed that the relative effect of chemotherapy was constant over the 10-year period in all patients, because there was no robust evidence to support a predictive impact of MammaPrint.[11,31,32] We did not take into account endocrine therapy, because the decision to administer such treatment is based on hormonal status. Using MammaPrint does not modify the decision of whether to administer hormone therapy. An additional analysis was performed in the subgroup of patients with ER-positive disease, because it could be argued that the potential clinical utility of the 70-gene profile would be mainly in the luminal subtype.[32]

Health Outcomes

Life-years (LYs) associated with each strategy were estimated using restricted mean survival at 10 years calculated from the Kaplan-Meier product-limit estimator[33] (weighted average of LYs in high- and low-risk patients). To account for the disutility associated with chemotherapy-induced toxicities and distant recurrence, we computed quality-adjusted life years (QALYs) using a partitioned survival analysis.[34] We considered four health states: the first year postsurgery with chemotherapy (free of distant recurrence or death), the first year postsurgery without chemotherapy (free of distant recurrence or death), distant recurrence–free survival, and survival after distant recurrence. For each of these health states, a utility value was extracted from a Swedish study,[35] which assessed quality of life in patients with breast cancer using the Euroqol EQ-5D questionnaire. We computed the restricted mean time in each health state from our clinical database using the Kaplan-Meier method. QALYs were then obtained as a weighted sum of average times in health states using mean utility values as weights.

Costs

The economic evaluation was conducted from the perspective of the French National Insurance Scheme, taking into account medical costs and sick leave compensations. We assumed that all high-risk patients would have received adjuvant chemotherapy. We estimated the cost of chemotherapy at €7,486 based on current unit costs for hospital stays and drugs in France and the PACS01 (Programme Adjuvant dans le Cancer du Sein) trial data[24,36] (Table 1). The cost of chemotherapy included the costs associated with drug administration, current drug costs, transportation costs, treatment of toxicities, biologic workup, and sick leave compensations paid by the national insurance scheme. We considered a FEC-D (three cycles of fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 followed by three cycles of docetaxel 100 mg/m^2) regimen for all women. For the MammaPrint strategy, we assumed that the MammaPrint test (€2,675) was performed in all patients. To take into account censorship, the cost of distant recurrences was obtained at the sample level by multiplying the Kaplan-Meier probability[38] of distant recurrence at 10 years by the cost of a distant recurrence from the perspective of the French National Insurance Scheme, which was extracted from a French study.[39] All costs are expressed in 2012 euros. Costs and health outcomes were discounted[40] at an annual rate of 4% according to French guidelines (Appendix, online only).

Cost-Effectiveness Analysis

We used the net monetary benefit approach[41] to overcome the limitations of estimating cost-effectiveness ratios in the presence of small differences in health outcomes (Appendix, online only). All cost-effectiveness results were computed using a combined bootstrap resampling technique and probabilistic sensitivity analysis[42] with 5,000 replicates. Such a method enables one to account for both patient variability and parameter uncertainty for costs, chemotherapy efficacy, and utility values (Appendix Table A1, online only). We computed the cost-effectiveness acceptability curves using the net monetary benefit approach for decisions involving multiple comparators.[43] Cost-effectiveness

Table 1. Unit Cost Data

Resource	Unit Cost (€)	Source
MammaPrint test	2,675	Agendia (Amsterdam, the Netherlands)
Adjuvant CT per patient		
CT administration (six cycles)	2,184	Diagnosis-related group 28Z07Z for CT administered in outpatient setting; mean tariff (weighted average of public and private for-profit hospital sector tariffs[37]) equal to €364 per cycle and covering cost of drugs
Venous port implantation	685	Diagnosis-related group 05K14Z tariff (weighted average of public and private for-profit hospital sector tariffs[37])
G-CSF	749	In 22% of patients (PACS01 trial; FEC-D arm), three injections of pelfilgrastim per patient[36]
Concomitant medication	342	Aprepitant (EMEND, Whitehouse Station, NJ; three cycles) and ondansetron (Zophren, Brentford, United Kingdom) orally (six cycles)
Transportation	240	Assumption: in 50% of patients, €80 per course
Biologic workup	219	Blood count, ionogram, hepatic test, biliburin, and creatinine per course; French national insurance system reimbursement tariffs
Cardiac ultrasound	96	French national insurance system reimbursement tariff
Acute toxicities	566	15% of patients experienced ≥ one serious adverse event (PACS01 trial)[36]; mean cost per hospital stay, €3,775 (French national cost survey; weighted cost of hospital stays for CT-induced hematologic toxicities)
Hair wigs	125	French national insurance reimbursement tariff
Sick leave	2,280	Assumption: in 40% of employed women, mean duration of sick leave attributable to chemotherapy, 5 months; mean compensation per day, €38 (French national insurance system)
Cost of chemotherapy	7,486	
Distant recurrence	36,516	Mean cost per patient from metastasis to death[38]

Abbreviations: CT, chemotherapy; FEC-D, fluorouracil, epirubicin, and cyclophosphamide followed by docetaxel; G-CSF, granulocyte colony-stimulating factor; PACS01, Programme Adjuvant dans le Cancer du Sein.

acceptability curves represent the probability of being the most cost effective for different values of the willingness of the national insurance scheme to pay for a QALY for each strategy. Sensitivity analyses were performed for the time horizon (15 years) and the cost of the MammaPrint test. We explored two options for the long-term chemotherapy effect. In the first option, we considered a constant HR of 0.67 over a 15-year period. In the second option, we assumed an HR of 0.67 over a 10-year period and an HR of 1 between 10 and 15 years. Finally, we carried out the cost-effectiveness analysis for the subgroup of patients with ER-positive disease. All analyses were performed using SAS software (version 9.2; SAS Institute, Cary, NC).

RESULTS

Base-Case Analysis: All Patients Over 10-Year Time Horizon

Without chemotherapy, 10-year overall survival was 77% (95% CI, 71% to 81%), and distant metastasis–free survival was 78% (95% CI, 73% to 83%). The proportion of high-risk patients was 72% in the Adjuvant! Online strategy and 63% in the MammaPrint strategy. Within a 10-year time horizon, health outcomes (LYs and QALYs) were similar between the three strategies (Table 2). Total cost across strategies ranged from €10,743 (95% CI, 4,578 to 35,225) for the Adjuvant! Online strategy to €12,780 (95% CI, 6,748 to 37,067) for the MammaPrint strategy. The uncertainty surrounding the cost-effectiveness results is presented in Figure 1. For a €50,000 per QALY willingness-to-pay threshold, the probability of being the most cost-effective strategy was 92% for the Adjuvant! Online strategy, 6% for the systematic chemotherapy strategy, and 2% for the MammaPrint strategy. The incremental net monetary benefit was significantly negative when the MammaPrint strategy was compared with the Adjuvant! Online strategy (Table 2); the MammaPrint strategy was not a cost-effective option at a €50,000 per QALY willingness-to-pay threshold.

Subgroup Analysis: Patients With ER-Positive Disease Over 10-Year Time Horizon

At 10 years, overall survival and distant metastasis–free survival were 82% (95% CI, 76% to 87%) and 83% (95% CI, 77% to 87%), respectively, in patients with ER-positive NNBC. The indications for adjuvant chemotherapy were fewer in this subgroup of patients compared with the base-case analysis. The proportion of high-risk

Table 2. Cost-Effectiveness Results in All Patients With 10-Year Time Horizon

	Cost (€)		LYs		QALYs		Cost Difference (€)*		Difference in LYs*		Difference in QALYs*		INMB (€)*	
Strategy	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
MammaPrint	12,780	6,748 to 37,067	7.74	7.60 to 7.87	5.90	5.73 to 6.06								
Adjuvant! Online	10,743	4,578 to 35,225	7.74	7.60 to 7.87	5.89	5.72 to 6.05	2,037	1,472 to 2,515	0.01	−0.01 to 0.03	0.02	−0.00 to 0.03	−1,275	−2,366 to −38
Systematic CT	12,123	6,080 to 34,189	7.77	7.63 to 7.89	5.88	5.71 to 6.04	657	−642 to 3,130	−0.02	−0.04 to −0.01	0.02	−0.04 to 0.06	560	−2,487 to 3,079

NOTE. 5,000 combined bootstrap and probabilistic sensitivity analysis replicates. Means and 95% CIs were estimated by bootstrap (percentiles) analysis. Costs are expressed in 2012 euros.

Abbreviations: CT, chemotherapy; INMB, incremental net monetary benefit; LY, life-year; QALY, quality-adjusted life-year.

*Differences and INMBs were calculated comparing MammaPrint strategy with either Adjuvant! Online or systematic CT. INMBs were calculated by valuing incremental QALYs generated by MammaPrint at €50,000 each (willingness-to-pay threshold) and subtracting incremental costs. MammaPrint strategy was cost effective if INMB > 0.

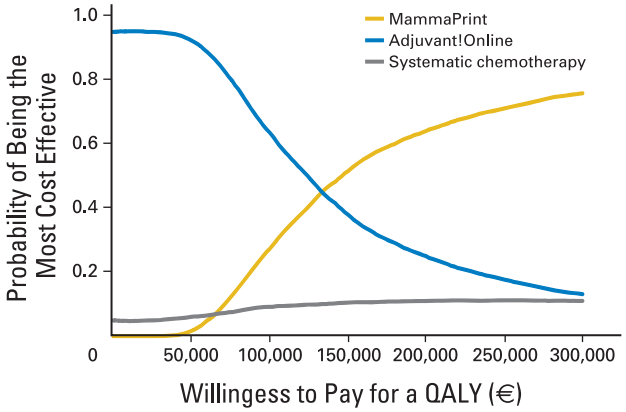

Fig 1. Cost-effectiveness acceptability curves using net–monetary benefit approach (5,000 bootstrap replicates) in all patients with 10-year time horizon. For each strategy, curve represents probability that strategy is most cost effective (highest net monetary benefit) at range of willingness-to-pay thresholds (euros per quality-adjusted life-year [QALY]), indicated by proportion of bootstrap replicates in which strategy has highest net benefit across all strategies among 5,000 replicates (sum of all probabilities at each willingness-to-pay threshold equals 1).

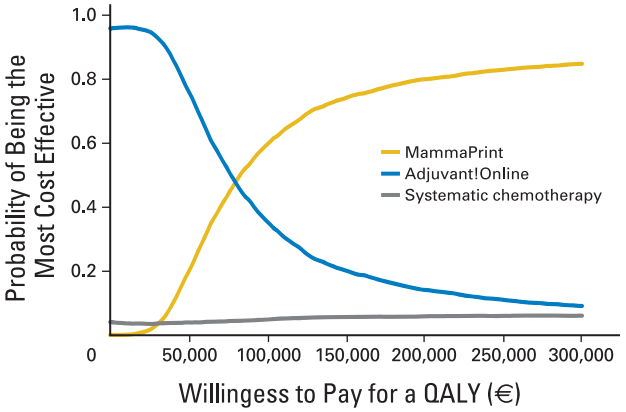

Fig 2. Cost-effectiveness acceptability curves using net–monetary benefit approach (5,000 bootstrap replicates) in estrogen receptor–positive patients only with 10-year time horizon. For each strategy, curve represents probability that strategy is most cost effective (highest net monetary benefit) at range of willingness-to-pay thresholds (euros per quality-adjusted life-year [QALY]), indicated by proportion of bootstrap replicates in which strategy has highest net benefit across all strategies among 5,000 replicates (sum of all probabilities at each willingness-to-pay threshold equals 1).

patients was 35% and 43% in the MammaPrint and Adjuvant! Online strategies, respectively. Health outcomes were similar among the three strategies (Table 3). The mean cost was significantly higher with the MammaPrint strategy compared with Adjuvant! Online strategy, with a difference in cost of €1,759 (95% CI, 881 to 2,419). For a €50,000 per QALY willingness-to-pay threshold, the probability of being the most cost-effective strategy was 76% for the Adjuvant! Online strategy, 20% for the MammaPrint strategy, and 4% for the systematic chemotherapy strategy (Fig 2).

Sensitivity Analysis

With a 15-year time horizon, the cost-effectiveness results for the MammaPrint strategy were similar to those of the base case (Appendix Tables A2 to A5, online only). For a €50,000 per QALY willingness-to-pay threshold, the probability of MammaPrint being the most cost-effective strategy varied between 2% and 5% for all patients with NNBC and between 19% and 26% for patients with ER-positive disease (Appendix Table A6, online only). Importantly, when the cost of the MammaPrint test was decreased (Appendix Table A7, online only), the cost-effectiveness results were more favorable toward the MammaPrint strategy (Fig 3).

DISCUSSION

Our economic evaluation suggests that the use of MammaPrint to select patients with NNBC at high risk of recurrence and to base adjuvant chemotherapy decision making on this criterion is not likely to be cost effective. Health outcomes were almost identical between the three strategies, and the MammaPrint strategy was associated with a significant extra cost when compared with Adjuvant! Online. The cost of the MammaPrint test seems to be too high in terms of the net health benefit it could procure if it were used in routine practice to guide treatment decision making.

Four economic studies[14,16,17,22] evaluated the cost effectiveness of MammaPrint. However, only two of these studies[14,16] quantified the uncertainty surrounding the cost-effectiveness results. Oestreicher et al[14] used clinical data from the first validation study of the 70-gene signature[44] in 295 patients with breast cancer. They found that MammaPrint was associated with a significant decrease in both QALYs and cost compared with the National Institutes of Health guidelines (96% of chemotherapy) using a lifetime horizon. Similarly, we found a decrease in QALYs between the MammaPrint strategy and systematic chemotherapy over a 15-year time horizon. In terms of cost, our

Table 3. Cost-Effectiveness Results in ER-Positive Patients With 10-Year Time Horizon

	Cost (€)		LYs		QALYs		Cost Difference (€)*		Difference in LYs*		Difference in QALYs*		INMB (€)*	
Strategy	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
MammaPrint	10,818	5,851 to 29,990	7.97	7.85 to 8.08	6.09	5.94 to 6.24								
Adjuvant! Online	9,059	3,899 to 28,452	7.96	7.84 to 8.07	6.07	5.91 to 6.22	1,759	881 to 2,419	0.01	−0.02 to 0.04	0.02	−0.00 to 0.05	−636	−2,240 to 1,167
Systematic CT	11,035	5,933 to 27,967	8.00	7.89 to 8.09	6.05	5.90 to 6.20	−216	−1,890 to 2,313	−0.02	−0.05 to −0.01	0.04	−0.01 to 0.09	2,148	−1,573 to 5,414

NOTE. 5,000 combined bootstrap and probabilistic sensitivity analysis replicates. Means and 95% CIs were estimated by bootstrap (percentiles) analysis. Costs are expressed in 2012 euros.

Abbreviations: CT, chemotherapy; ER, estrogen receptor; INMB, incremental net monetary benefit; LY, life-year; QALY, quality-adjusted life-year.

*Differences and INMBs were calculated comparing MammaPrint strategy with either Adjuvant! Online or systematic CT. INMBs were calculated by valuing incremental QALYs generated by MammaPrint at €50,000 each (willingness-to-pay threshold) and subtracting incremental costs. MammaPrint strategy was cost effective if INMB > 0.

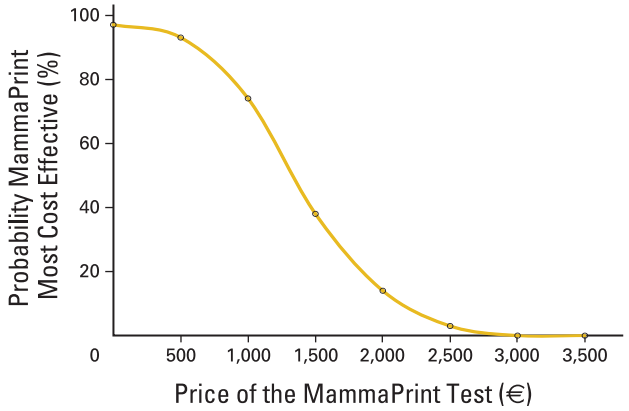

Fig 3. Probability that MammaPrint is most cost-effective strategy for different test prices, with 10-year time horizon and 5,000 combined bootstrap and probabilistic sensitivity analysis replicates for each price for €50,000 per quality-adjusted life-year (QALY) willingness-to-pay threshold. Higher MammaPrint price (€3,500) was considered to take into account 27% test failure rate (test performed but not exploitable for decision making), as observed in RASTER (Microarray Prognostics in Breast Cancer) study.

results showed significantly higher costs with the MammaPrint strategy. With the availability of a generic version of Taxotere (docetaxel; sanofi-aventis, Paris, France), the cost of chemotherapy has decreased. Consequently, the savings obtained by the reduction in the number of chemotherapy treatments used in the MammaPrint strategy do not outweigh the cost of the test performed in all patients. The second study by Retel et al[16] compared MammaPrint with Adjuvant! Online and the St Gallen guidelines over 20 years. MammaPrint had the highest probability of being cost effective. The sensitivity and specificity of the test were estimated in a subsample of 308 patients with ER-positive disease selected from the three validation studies of MammaPrint,[26,44,45] using 10-year breast cancer survival as a final outcome. The probabilities of distant metastasis and death were derived from published literature and were not estimated from the same population. Patients classified as true low and false high were assumed to have a zero probability of relapse and distant metastasis. It was assumed that low-risk patients could not die as a result of breast cancer. It was unclear how the effect of chemotherapy was introduced in the model. The cost of chemotherapy was higher than ours, because 10% of the women were considered to have received trastuzumab. Finally, the follow-up cost in high-risk patients was assumed to be twice that of low-risk patients. All these assumptions were in favor of the MammaPrint strategy.

Our study has some limitations. First, we chose to consider two comparators: a binary version of Adjuvant! Online and systematic chemotherapy. This choice was guided by previous economic studies and the absence of a reference strategy for adjuvant chemotherapy indications in patients with NNBC in France. No reliable data on medical practices were available enabling us to consider a current practice strategy in this population. We considered that a strategy based on the use of Adjuvant! Online represented the current practice of oncologists. Adjuvant! Online was used as a classification tool in the validation studies of the 70-gene signature,[27,46] in the prospective MINDACT (Microarray in Node-Negative Disease May Avoid Chemotherapy) trial,[47] and in recent clinical studies.[46,48-51] However, it is difficult to know whether the current practices are totally consistent with Adjuvant! Online. Because most patients with NNBC are likely to be treated in France, we decided to consider systematic chemotherapy in all women as a possible option to assess the cost effectiveness of MammaPrint. Second, we included all patients with NNBC as the target population for the base-case analysis. This choice was consistent with the population investigated in validation studies.[26,44,45] However, most clinical guidelines restrict the use of validated multigene tests. For the European St Gallen International Expert Consensus (2009),[52] these tests are considered helpful in decision making regarding adjuvant chemotherapy in cases where its use was uncertain after consideration of conventional markers. Recent National Comprehensive Cancer Network guidelines also restrict the use of the 21-gene real-time polymerase chain reaction assay to specific subgroups of patients for further decision making regarding adjuvant treatment.[53] We therefore performed a sensitivity analysis in patients with ER-positive NNBC. Third, we were unable to take into account long-term adverse events resulting from chemotherapy and their impact on quality of life, given the paucity of available data. In a phase III adjuvant trial comparing doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in patients with node-positive, human epidermal growth factor receptor 2–positive disease, cardiac events occurred in 1.3% of control patients after 7 years of follow-up.[54] However, we found no studies in which disutility associated with such long-term adverse events had been estimated. Our analysis is therefore likely to underestimate the incremental net benefit associated with the MammaPrint strategy when compared with systematic chemotherapy. Finally, our results were based on a small–sample size study of young patients with NNBC (mean age, 47 years), with a median follow-up of 13.6 years. With this limited amount of data, we were unable to calculate reliable survival predictions over the lifetime horizon. We therefore decided to use a 10-year time horizon in the base-case analysis and to study the robustness of our results with a longer time horizon of 15 years. The results of this sensitivity analysis confirmed the base-case analysis and suggested that a longer time horizon might not translate into better cost-effectiveness results for the MammaPrint strategy. The patients included in the TRANSBIG consortium study may not be truly representative of current patients with NNBC. This might limit the generalizability of our results. However, this multinational study has the longest follow-up available to assess the performances of MammaPrint without the confounding effects of treatment.

In conclusion, treatment de-escalation is critical for ensuring high-quality survivorship over the long term. International research efforts have enabled the identification of patient subgroups based on molecular profiles that have subsequently been developed as clinical decision-making tools. Such progress should lead to better patient-tailored therapy and enable clinicians to optimize the clinical risk/benefit ratio of the treatments they administer. However, our study shows that the health benefits associated with the use of molecular tests are modest. In addition, the high price of these tests results in poor value for money, limiting their usefulness in routine practice.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Julia Bonastre
Provision of study materials or patients: Stefan Michiels, Suzette Delaloge
Collection and assembly of data: Julia Bonastre, Stefan Michiels, Suzette Delaloge
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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GLOSSARY TERMS

biomarker: a functional biochemical or molecular indicator of a biologic or disease process that has predictive, diagnostic, and/or prognostic utility.

bootstrap resampling technique: an analytical tool that evaluates how robust the associations are between the specimens under evaluation on the basis of the gene profiles. The higher the number provided by this method, the more robust the associations.

genomic signatures: the expression of a set of genes in a biologic sample (eg, blood, tissue) using microarray technology.

predictive impact: a measurable patient characteristic that is associated with the degree of response to therapy. The predictive impact of a factor refers to that part of its influence on the subsequent course of disease that is attributable to its association with therapy response. The impact of a factor can be prognostic, predictive, or both.

prognostic factor: a measurable patient characteristic that is associated with the subsequent course of disease (whether or not therapy is administered). The identification of a prognostic factor does not necessarily suggest a cause-and-effect relationship. However, within a suitable outcome model, the measurement of a prognostic factor contributes to an estimate of an outcome probability (eg, the probability of disease-free survival within a given time interval).

validation: the process that tests the performance of a previously defined classifier or prognostic model on a new set of patients. For example, a gene expression signature classifier developed using data from one set of patients might be validated on another, independent set of patients.

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Appendix

Modeling of Effect of Chemotherapy

None of the patients in the validation study by Buyse et al[26] received adjuvant chemotherapy. The absolute risk reduction afforded by chemotherapy against distant recurrence and death resulting from breast cancer was estimated using the method of Stewart et al.[30] Under the proportional hazards assumption, the survival function in the experimental group is defined as $S_{exp}(t) = S_{control}(t)^{HR}$ where $S_{control}$ represents the survival function in the control group estimated with the Kaplan-Meier method and the hazard ratio (HR) of the treatment effect.

We calculated an HR corresponding to the indirect comparison of a taxane regimen with no chemotherapy (control) using data from the Early Breast Cancer Trialists' Collaborative Group: $HR_{\text{taxane } v \text{ no chemotherapy}} = 0.67$ (95% CI, 0.51 to 0.88). To model the efficacy of a strategy (chemotherapy exclusively in high-risk patients), we applied this HR to the survival functions in high-risk patients estimated from our data over a 10-year period and assumed an HR of 1 after 10 years.

Discounting Method for Health Outcomes

On the basis of the study by Sassi,[40] we used the following formula to discount quality-adjusted life-years (QALYs):

$$Discounted\ QALYs = \sum_{i=1}^{N} u_i \frac{e^{-r(t_{i-1}-t_0)} - e^{-r(t_i-t_0)}}{r}$$

Where N is the number of consecutive health states used in the economic evaluation; u_i $(i = 1 \ldots N)$ is the utility value associated with the health state i; t_0 is the time point that delimits the beginning of the first health state; t_i $(i = 1 \ldots N)$ is the time point that delimits the end of the health state i; and r is the discount rate.

To discount life-years, we used the above equation considering only one health state and no utility weights:

$$Discounted\ LYs = \frac{1 - e^{-r(t_N-t_0)}}{r}$$

Calculation of Net Monetary Benefit

Net monetary benefit was calculated by assuming a €50,000 per QALY willingness-to-pay threshold to convert QALYs into the common metric of euros. The cost associated with each strategy was then subtracted, resulting in the net benefit of each strategy expressed in the monetary units.

$$\text{Net monetary benefit} = \text{QALYs} \times \text{WTP} - \text{COST}$$

Where WTP = willingness-to-pay threshold. The net monetary benefit framework was used to rank the most cost-effective strategy among the three strategies compared and to compute cost-effectiveness acceptability curves. For each strategy, a curve represents the probability that the strategy is the most cost effective (highest net monetary benefit) at a range of willingness-to-pay thresholds (euros per QALY).

The incremental net monetary benefit of the MammaPrint strategy relative to either Adjuvant! Online or systematic chemotherapy was obtained as follows:

$$\text{Inremental net monetary benefit} = \Delta\ \text{QALYs} \times \text{WTP} - \Delta\ \text{COST}$$

Where Δ QALYs = difference in QALYs between two strategies; Δ COST = cost difference between two strategies; and WTP = willingness-to-pay threshold.

Table A1. Assumed Distributions and Parameters Used in Probabilistic Sensitivity Analysis

Parameter	Deterministic Value	Distribution	Source
Cost of adjuvant CT	7,486	LN (8.84, 0.16)	Assumption
Cost of distant recurrence	36,516	LN (10, 1.2)	Bonastre et al[39]
Utility values			Hall et al,[23] Ward et al[31]
Free of disease			
First year with CT	0.62	Beta (182, 111)	
First year without CT	0.74	Beta (76, 26)	
Subsequent years	0.78	Beta (1,782, 506)	
Distant recurrence	0.69	Beta (537, 247)	
Assumed treatment effect of CT	0.67	LN (−0.42, 0.04)	Peto et al,[4] Early Breast Cancer Trialists' Collaborative Group[29]

Abbreviations: CT, chemotherapy; LN, log-normal distribution.

Table A2. Cost-Effectiveness Results in All Patients With 15-Year Time Horizon

	Cost (€)		LYs		QALYs		Cost Difference (€)*		Difference in LYs*		Difference in QALYs*		INMB (€)*	
Strategy	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
MammaPrint	13,497	6,812 to 41,303	10.16	9.89 to 10.40	7.79	7.53 to 8.03								
Adjuvant! Online	11,463	4,647 to 38,789	10.16	9.89 to 10.40	7.78	7.52 to 8.02	2,034	1,396 to 2,594	0.00	−0.05 to 0.05	0.01	−0.02 to 0.05	−1,404	−3,229 to 496
Systematic CT	13,012	6,165 to 39,159	10.18	9.93 to 10.42	7.77	7.50 to 8.01	485	−709 to 2,239	−0.03	−0.05 to 0.01	0.02	−0.02 to 0.07	632	−2,011 to 3,289

NOTE. 5,000 combined bootstrap and probabilistic sensitivity analysis replicates. Means and 95% CIs were estimated by bootstrap (percentiles) analysis. Costs are expressed in 2012 euros. HR for CT was 0.67 until 10 years and 1 afterward.
Abbreviations: CT, chemotherapy; HR, hazard ratio; INMB, incremental net monetary benefit; LY, life-year; QALY, quality-adjusted life-year.
*Differences and INMBs were calculated comparing MammaPrint strategy with either Adjuvant! Online or systematic CT. INMBs were calculated by valuing incremental QALYs generated by MammaPrint at €50,000 each (willingness-to-pay threshold) and subtracting incremental costs. MammaPrint strategy was cost effective if INMB > 0.

Table A3. Cost-Effectiveness Results in ER-Positive Patients With 15-Year Time Horizon

	Cost (€)		LYs		QALYs		Cost Difference (€)*		Difference in LYs*		Difference in QALYs*		INMB (€)*	
Strategy	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
MammaPrint	11,326	5,911 to 33,365	10.49	10.25 to 10.73	8.06	7.81 to 8.31								
Adjuvant! Online	9,549	3,939 to 32,122	10.48	10.24 to 10.72	8.04	7.79 to 8.28	1,778	919 to 2,438	0.01	−0.04 to 0.06	0.02	−0.01 to 0.06	−587	−2,695 to 1,827
Systematic CT	11,631	6,014 to 31,577	10.52	10.29 to 10.74	8.02	7.78 to 8.27	−305	−1,915 to 2,032	−0.03	−0.06 to 0.01	0.04	−0.02 to 0.10	2,260	−1,481 to 5,745

NOTE. 5,000 combined bootstrap and probabilistic sensitivity analysis replicates. Means and 95% CIs were estimated by bootstrap (percentiles) analysis. Costs are expressed in 2012 euros. HR for CT was 0.67 until 10 years and 1 afterward.
Abbreviations: CT, chemotherapy; ER, estrogen receptor; HR, hazard ratio; INMB, incremental net monetary benefit; LY, life-year; QALY, quality-adjusted life year.
*Differences and INMBs were calculated comparing MammaPrint strategy with either Adjuvant! Online or systematic CT. INMBs were calculated by valuing incremental QALYs generated by MammaPrint at €50,000 each (willingness-to-pay threshold) and subtracting incremental costs. MammaPrint strategy was cost effective if INMB > 0.

Table A4. Cost-Effectiveness Results in All Patients With 15-Year Time Horizon

	Costs (€)		LYs		QALYs		Cost Difference (€)*		Difference in LYs*		Difference in QALYs*		INMB (€)*	
Strategy	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
MammaPrint	13,255	6,800 to 39,928	10.31	10.08 to 10.52	7.91	7.66 to 8.14								
Adjuvant! Online	11,033	4,598 to 36,775	10.31	10.07 to 10.52	7.89	7.65 to 8.12	2,221	1,626 to 3,160	0.01	−0.03 to 0.05	0.01	−0.01 to 0.04	−1,531	−3,252 to 147
Systematic CT	12,462	6,105 to 36,284	10.38	10.16 to 10.58	7.92	7.68 to 8.15	792	−607 to 3,954	−0.07	−0.10 to −0.04	−0.01	−0.06 to 0.03	−1,420	−5,130 to 1,378

NOTE. 5,000 combined bootstrap and probabilistic sensitivity analysis replicates. Means and 95% CIs were estimated by bootstrap (percentiles) analysis. Costs are expressed in 2012 euros. HR for CT is 0.67 over 15 years.

Abbreviations: CT, chemotherapy; HR, hazard ratio; INMB, incremental net monetary benefit; LY, life-year; QALY, quality-adjusted life-year.

*Differences and INMBs were calculated comparing MammaPrint strategy with either Adjuvant! Online or systematic CT. INMBs were calculated by valuing incremental QALYs generated by MammaPrint at €50,000 each (willingness-to-pay threshold) and subtracting incremental costs. MammaPrint strategy was cost effective if INMB > 0.

Table A5. Cost-Effectiveness Results in ER-Positive Patients With 15-Year Time Horizon

	Cost (€)		LYs		QALYs		Cost Difference (€)*		Difference in LYs*		Difference in QALYs*		INMB (€)*	
Strategy	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
MammaPrint	11,180	5,895 to 32,084	10.60	10.38 to 10.80	8.14	7.90 to 8.38								
Adjuvant! Online	9,256	3,913 to 30,286	10.58	10.36 to 10.79	8.12	7.88 to 8.35	1,925	1,144 to 2,730	0.01	−0.04 to 0.08	0.03	−0.02 to 0.07	−673	−3,190 to 1,828
Systematic CT	11,271	5,959 to 29,566	10.68	10.49 to 10.86	8.15	7.92 to 8.37	−91	−1,835 to 3071	−0.08	−0.13 to −0.04	−0.01	−0.07 to 0.05	−234	−4,556 to 3,402

NOTE. 5,000 combined bootstrap and probabilistic sensitivity analysis replicates. Means and 95% CIs were estimated by bootstrap (percentiles) analysis. Costs are expressed in 2012 euros. HR for CT is 0.67 over 15 years.

Abbreviations: CT, chemotherapy; ER, estrogen receptor; HR, hazard ratio; INMB, incremental net monetary benefit; LY, life-year; QALY, quality-adjusted life-year.

*Differences and INMBs were calculated comparing MammaPrint strategy with either Adjuvant! Online or systematic CT. INMBs were calculated by valuing incremental QALYs generated by MammaPrint at €50,000 each (willingness-to-pay threshold) and subtracting incremental costs. MammaPrint strategy was cost effective if INMB > 0.

Table A6. Probability of Strategy Being Most Cost Effective for €50,000 per QALY Willingness-to-Pay Threshold for All Patients Over 15-Year Horizon

Chemotherapy Effect > 10 Years (HR)	MammaPrint (%)	Adjuvant! Online (%)	Systematic CT (%)
0.67	2	57	42
1	5	91	4

Abbreviations: CT, chemotherapy; HR, hazard ratio; QALY, quality-adjusted life-year.

Table A7. Probability of Strategy Being Most Cost Effective for €50,000 per QALY Willingness-to-Pay Threshold for ER-Positive Patients Over 15-Year Horizon

Chemotherapy Effect > 10 Years (HR)	MammaPrint (%)	Adjuvant! Online (%)	Systematic CT (%)
0.67	19	50	31
1	26	71	3

Abbreviations: CT, chemotherapy; ER, estrogen receptor; HR, hazard ratio; QALY, quality-adjusted life-year.