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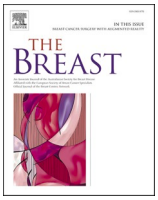

# Impact of the genomic signature of 70-genes for breast cancer in the public system and in supplementary health care in a country of medium socioeconomic development

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ABSTRACT

*Introduction:* The financial impact of breast cancer has been discussed due to its high incidence and the increased costs of systemic therapy and is even more relevant in countries with low and medium socioeconomic development.
*Objective:* To evaluate the financial viability of using the MammaPrint™ (MP) genetic signature in a public and private system in a country with a medium socioeconomic development index.
*Material and method:* A pharmacoeconomic trial with a cost-benefit analysis evaluating the reduction in costs of chemotherapy, support drugs, and materials used during chemotherapy infusion in high-risk hormone receptor-positive (HR+) breast cancer patients submitted to analysis using the MammaPrint™ genetic signature.
*Results:* The value of using MammaPrint™ in the Unified Health System (SUS) would bring an additional cost of US$ 1,334.56 per patient in the over-50 age group. In private medicine, the use of MammaPrint™ in the same population would result in cost savings ranging from US$ 2,422.53 to US$ 9,989.95 per patient.
*Conclusion:* The use of MP in RH + breast cancer patients with high clinical risk and low genomic risk in Brazil leads to significant savings in resources when applied to supplementary healthcare. In the SUS, reducing the costs of MP for large-scale use could make its application viable. These values need to be re-evaluated in each institution, using the methodology applied in the trial, adjusting according to costs, to obtain a result that reflects its reality.

## 1. Introduction

Because breast cancer is the most common malignant neoplasm in women worldwide, it is associated with financial impacts on health spending in all countries, and this cost is even more relevant when we talk about those with medium and low socioeconomic development [1]. In this context, around 70 % of breast cancer cases are hormone receptor-positive and HER2-negative (luminal) tumors, whose preferred systemic therapy is hormonal manipulation (endocrine therapy) [2], but part of this universe, due to its high clinical risk, also receives chemotherapy in the adjuvant or neoadjuvant setting.

To identify among luminal patients at high clinical risk those who would not benefit from the addition of antineoplastic cytotoxic therapy, genetic signatures were developed [3] which, by evaluating genes related to proliferation, metastasis, and other behaviors linked to a high risk of recurrence, would select patients who could be spared chemotherapy [4,5].

In this context, the 70-genes signature (MammaPrint™), by identifying patients at low genomic risk, makes it possible to de-escalate chemotherapy treatment in this population [4,6]. The phase III study that approved the 70-genes platform (MINDACT), carried out in a European cohort of 3,356 patients with luminal breast cancer at high clinical risk, showed low genomic risk in around 46 % of patients, and when systemic treatment was de-escalated by withdrawing chemotherapy from these patients, there was no significant reduction in the distant metastasis-free survival rate in the low genomic risk population submitted to endocrine therapy alone [4].

Another study carried out in a Brazilian population (AGEMA-BRA), evaluated 953 hormone receptor-positive, HER2-negative breast cancer patients at high clinical risk who underwent MammaPrint™ (MP)

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genetic signature. Data analysis found 542 (57.2 %) patients with low genomic risk, a result which indicates the even greater possibility of mismatch cited in the MINDACT study [7]. In the same publication, an analysis was carried out in the age group ≥50 years and found low genomic risk in 59.8 %.

Similarly, in a trial conducted with another genetic signature in two centers in São Paulo (Brazil), a 63 % reduction in the indication for adjuvant chemotherapy was observed [8]. However, to date, no pharmacoeconomic trial has been conducted with any of these genetic signatures in Brazil.

Updated data from the MINDACT trial, with an eight-year follow-up, showed a 5 % benefit rate from the use of chemotherapy in the under-50 population, which makes this scenario unsuitable for the application of MammaPrint™ in therapy de-escalation in this age group [9].

Intending to assess the financial viability, based on pharmacoeconomic analysis, in a country with a medium socioeconomic development index, of using the 70-genes signature in public and private medicine, we designed this trial [10–13].

## 2. Materials and methods

A pharmacoeconomics trial, with cost-benefit analysis [14], evaluated the impact of the 70-genes signature on the financial cost of chemotherapy in women with clinically high-risk luminal tumors in Brazil. The investigation was based on the possibility of omitting chemotherapy in a percentage of women with low genomic risk and aged over 50, according to the long-term results of the MINDACT trial [9]. Our initial hypothesis was that the addition of the test could reduce the costs of systemic treatment in the country, both in the public and private health systems.

### 2.1. Calculating financial costs

The treatment regimens recommended by the National Comprehensive Cancer Network (NCCN) for adjuvant chemotherapy of patients with hormone receptor-positive, HER2-negative breast tumors, version 4.2023, were examined [15]. To calculate the dose of chemotherapy used, a body surface area of 1.69 $m^2$ was considered, according to the publication by Martins et al. (2012) [16].

To estimate costs in the SUS, we used the monthly amounts paid in July 2023 for the adjuvant treatment of stage II breast cancer code from the Brazilian Ministry of Health's System for Managing the Table of Procedures of the Unified Health System (SIGTAP) (Supplementary material - Fig. 1) [17]. The amounts include chemotherapy, support drugs and materials used during infusion, use of the infrastructure and care provided by the nursing team during the patient's stay in the infusion unit.

For the Supplementary Health calculation, we used the protocols of the *Instituto Sul Paranaense de Oncologia* in Ponta Grossa, Brazil (ISPON). The values of the medicines and materials used were taken from the BRASÍNDICE, edition of the 2nd half of July 2023 [18]. As this is a cost-benefit trial, estimates of the social impact, labor, and indirect costs

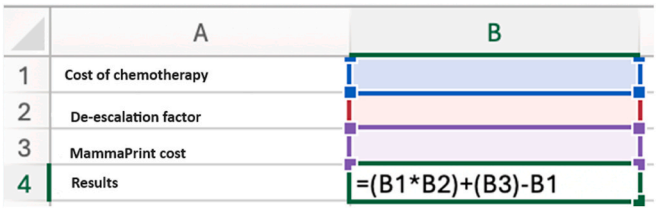


**Fig. 1.** Formula for calculating chemotherapy costs using the 70-genes platform. Chemotherapy cost (values of drugs and materials at the time of infusion; De-escalation factor (all patients 0.427, ≥50 years 0.402, <50 years 0.462); MammaPrint cost (marketing value of the platform); Result (negative number corresponds to resource savings, positive number to cost increase).

of treatment and its complications, among others, were not included.

The cost of the MammaPrint™ genetic signature corresponds to the average price charged by its distributors in Brazil (GenCell Pharma and Precision Medicine) in July 2023 (US$ 2,100.00). Costs were converted into Brazilian reals and US dollars at the approximate average exchange rate over the last 12 months, i.e. US$ 1.00 = R$ 5.00.

After calculating the individual cost, a financial feasibility simulation was carried out using data from the AGEMA-BRA study [7]. This is a retrospective cohort selected consecutively between 2016 and 2020 through GenCell Pharma's central bank of tests in Brazil. Patients with initial HR-positive, and HER2-negative breast cancer at high clinical risk from all regions of the country were included. In the end, 953 patients were included, of whom 637 (67 %) were over 50 years old and 546 (57 %) had a low genomic risk for MammaPrint™ (AGEMA-BRA study) [7].

The high genomic risk was used to calculate the de-escalation factor, which corresponds to 40.2 % in the 50+ age group, 46.2 % under 50, and 42.7 % for all ages.

Based on the results observed in this study, a de-escalation factor was calculated, which corresponds to the percentage of patients who would undergo chemotherapy because they have a high genomic risk of MP, which for the population aged ≥50 years corresponds to 0.402. If it is of interest, the de-escalation factor can be used for all ages (0.427) and the <50 age group (0.462).

To obtain the financial result, a spreadsheet is used according to the model shown in Fig. 1, where the cost of QT is the total value of the drugs and materials used in all chemotherapy cycles, the de-escalation factor according to age group, the cost of the MP and the rest of the chemotherapy.

### 2.2. Ethical aspects

The trial was approved by the institution's Ethics Committee, according to protocol (CAAE) number 12194219.4.0000.0105, technical advice 5.707.195 (Supplementary material – attachment 1). All the recommendations of good clinical practice and Brazil's General Data Protection Law (LGPD) were followed.

This research received financial support from GenCell Pharma (MammaPrint™ distributor in Brazil).

## 3. Results

Considering the population included (high clinical risk, low genomic risk), we observed a possibility of downgrading the indication for adjuvant chemotherapy by 57.3 %. When only the age group ≥50 years is evaluated, this reduction reaches 59.8 % (Fig. 1).

In the Brazilian public system, the reimbursement amount for chemotherapy is fixed and corresponds to US$ 160.00 per cycle, regardless of the medications used, clinical stage, or histological subtype. Considering the total of eight cycles released, this gives US$ 1,280.00 per patient treated [19]. Applying the MP to the public system population would reduce the cost of chemotherapy to US$ 549.00 and in the population ≥50 years to US$ 514.56. Added to the cost of the 70-genes subscription, this amounts to a total of US$ 2,649.00 and US$ 2,614.56 per patient, respectively. Thus, the use of MP in the SUS would bring an additional cost of US$ 1,371.20 per patient and in the age group over 50 years US$ 1,344.40.

In order to assess the outlay for supplementary healthcare, we surveyed the costs of the main regimens used for high clinical risk luminal tumors - TC (Docetaxel + Cyclophosphamide for 4 or 6 cycles, every 21 days), AC-Tsem (Doxorubicin + Cyclophosphamide for 4 cycles, every 21 days, followed by weekly Paclitaxel for 12 weeks) and ddAC-Tsem (Doxorubicin + Cyclophosphamide in dense dose + granulocyte colony growth factor, every 14 days, followed by weekly Paclitaxel for 12 weeks) [15] (Table 1). The detailed cost calculation is described in attachment 3 (supplementary material).

Using the TC regimen (docetaxel + cyclophosphamide) with four

**Table 1**
Values of adjuvant chemotherapy regimens in the supplementary health system.

| Protocol | 1 cycle | 4 cycles | Total Per Patient[a] |
|---|---|---|---|
| TC (Docetaxel + Cyclophosphamide) | US$ 1,890.69 | US$ 7,562.76 | US$ 7,562.76<br>US$ 11,344.14 (6 cycles) |
| AC-Tw 1st Phase (Doxorubicin + Cyclophosphamide) | US$ 500.04 | US$ 2,000.16 | |
| AC-Tw 2nd Phase (Pacitaxel) | US$ 3,862.44 (3 weekly doses) | US$ 15,449.76 | US$ 17,449.92 (1st + 2nd phase) |
| DDAC-Tw 1st Phase (Doxorubicin + Cyclophosphamide + Filgrastim) | US$ 1,191.85 | US$ 4,767.40 | |
| DDAC-Tw 2nd Phase (Paclitaxel) | US$ 3,862.44 (3 weekly doses) | US$ 15,449.76 | US$ 20,217.32 (1st + 2nd phase) |

[a] Detailed description of costs available in Supplementary Material Figs. 3–5.

cycles every 21 days, the cost per patient would be US$ 7,562.76. By using the 70-genes platform and applying the 59.8 % de-escalation, the cost per patient would be reduced to US$ 5,140.23, an average saving in resources spent per patient of US$ 2,422.53 in the population aged over 50.

When the AC-Tw protocol is indicated, with an average cost of US$ 17,449.92, applying the reduction in the indication of chemotherapy in the low genomic risk population aged >50 years would reduce the amount spent by around US$ 8,335.56 per patient. If the dense dose protocol were used, the reduction in costs in this same population would reach US$ 9,989.95. The figures for the other populations are detailed in Table 2.

## 4. Discussion

As has been known for decades, most patients undergoing adjuvant chemotherapy for breast cancer receive this toxic medication without benefiting from it [20]. Therefore, they are exposed to the morbidity and even mortality inherent in the treatment, in addition to the financial toxicity of both the treatment and its complications.

In our trial, we sought to investigate the financial viability of the cost-benefit method, following the structural conditions of Brazilian healthcare, where cancer treatments are available in both the public and private spheres.

Pharmacoeconomics studies are essential for incorporating new drugs and technologies into clinical practice and the coverage role of health regulatory agencies [21]. To our knowledge, this trial corresponds to the first survey of pharmacoeconomics involving the signature of 70-genes and the indication of adjuvant chemotherapy in Brazil, the main results of which were: (i) an increase in the overall financial cost of incorporating PM into the public health system; (ii) a reduction in the overall financial cost in the private health system, regardless of the chemotherapy regimen used (Fig. 2).

A pharmacoeconomic analysis was carried out on the entire cohort of the AGEMA-BRA study, which showed an overall reduction in costs, but since the publication of the MINDACT study update, oncological safety has only been achieved in the population aged 50 or over, which would correspond to post-menopausal status, limiting the application of the signature [9].

In Brazil, around 70 % of the population uses and depends on the public health system [22]. This is a population with socioeconomic restrictions and, consequently, high rates of palpable tumors or tumors with a compromised armpit at diagnosis [23]. They also experience delays in starting treatment and barriers to accessing gold standard therapies [23,25]. Thus, the 59.8 % downgrading of the indication for adjuvant chemotherapy using the genetic signature could represent a bridge towards reducing the social impact of breast cancer treatment in low- and middle-income countries [13,26], without harming distant metastasis-free survival [6].

Considering the cost-benefit analysis carried out, the incorporation of the genetic signature into the SUS will generate a significant increase in the individual cost per treatment. This is probably due to the reimbursement model used, in which the Federal Government pays a fixed amount, regardless of what is used [19]; this, in turn, is outdated and below the average values practiced in the private system. Despite this, we believe that the financial viability of MammaPrint™ in the SUS can still be demonstrated through a cost-effectiveness trial, which includes the impact on work, the cost of travel, exams, and consultations, as well as the management of adverse events during chemotherapy. In addition, a broad discussion involving public institutions and the distributors of the genetic signature in the country could reduce the cost of implementation to levels that can be supported by the annual SUS budget.

In the supplementary health system, the financial costs of chemotherapy are skyrocketing and justify the addition of the 70-genes signature to the care protocol for patients with high-risk luminal tumors. In this way, the reduction in financial cost through MammaPrint™ could offset the overall increase in the cost of treatment seen in recent years, contributing, as in the public system, to a better distribution of the resources involved and greater access to other medications [27,28]. In clinical practice, this incorporation comes up against the National

**Table 2**
Description of the pharmacoeconomic calculation of the MammaPrint® application in the AGEMA-BRA[a] population.

| | TC (×4) | TC (×6) | AC-Tw | ddAC-Tw |
|---|---|---|---|---|
| *All ages* | | | | |
| *QT* | 7,562.76 | 11,344.14 | 17,449.92 | 20,217.32 |
| *QT + MP* | 5,329.29 | 6,943.94 | 9,551.12 | 10,732.79 |
| *Result* | 2,233.46 | 4,400.19 | 7,898.80 | 9,484.52 |
| *≥ 50 years old* | | | | |
| *QT* | 7,562.76 | 11,344.14 | 17,449.92 | 20,217.32 |
| *QT + MP* | 5,140.23 | 6,660.34 | 9,114.87 | 10,227.36 |
| *Result* | 2,422.53 | 4,684.19 | 8.335,05 | 9,989.95 |
| *<50 years old* | | | | |
| *QT* | 7,562.76 | 11,344.14 | 17,449.92 | 20,217.32 |
| *QT + MP* | 5,593.99 | 7,340.99 | 10,161.86 | 11,440.40 |
| *Result* | 1,968.76 | 4,003.14 | 7,288.06 | 8,776.91 |

[a] Values in US dollar. QT (cost of chemotherapy - drugs and materials used in the infusion), QT + PM (average value considering the costs of chemotherapy, PM used in all patients), Result (average cost considering the de-escalation by band would be). TC - docetaxel and cyclophosphamide, AC-Tsem - doxorubicin and cyclophosphamide and weekly paclitaxel, ddAC-Tsem - includes dense dose.

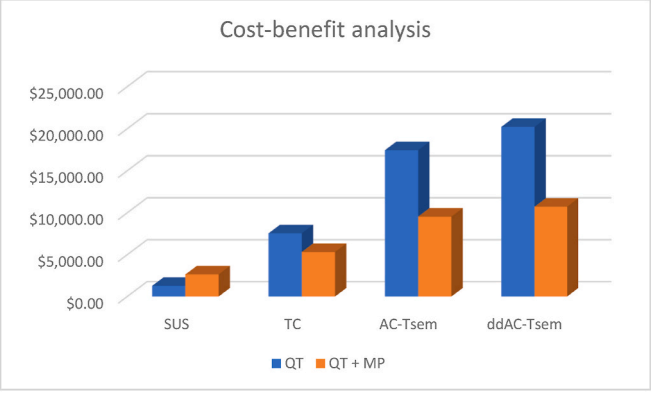


**Fig. 2.** Comparative analysis of chemotherapy costs with and without the use of MammaPrint ™ in the public and private systems. SUS – Unified Health System; TC – Docetaxel + Cyclophosphamide; AC-Tsem – Doxorubicin + Cyclophosphamide followed by weekly Paclitaxel; ddAC-Tsem – Doxorubicin + Cyclophosphamide in dense dose followed by weekly Paclitaxel. QT – chemotherapy; QT + MP – chemotherapy plus MammaPrint™.

Health Agency (ANS); a government institution that regulates health plans in Brazil and draws up a list of drugs, procedures, and technologies that must be covered [21]. In this context, we believe that our trial could help to investigate the financial viability of genetic signatures in the country, especially in women over 50.

One of the limitations of this trial is the way chemotherapy is reimbursed and paid for by the SUS, which may have hindered the analysis of pharmacoeconomics in this scenario. However, although outdated, it corresponds to what is carried out in clinical practice. About the private system, it should be noted that the values adopted came from a single cancer treatment center, which may not represent the reality of the prices practiced in other centers. This could be because prices are subject to variations according to financial negotiations with the industry and the supplementary health company (for example, lower costs when buying centrally or in greater volume). We therefore suggest that the calculations be repeated for each center and each geographical region, to confirm the results found in our trial. Finally, about the sample used to calculate financial viability, we would emphasize the retrospective nature of the data collection. Despite this, AGEMA-BRA is a representative cohort of the entire Brazilian territory, with more than 40 months of follow-up and data in line with the MINDACT trial [6,7].

Another significant limitation of the study is linked to the way the costs were collected, although pre-planned, where we used cost-benefit and not cost-effectiveness, thus tabulating only the direct costs at the time of infusion, we underestimated the real values, although when we find results that demonstrate the financial viability of the test, we are assuring its benefit, but without knowing its value.

To understand the impact of MammaPrint™ in Brazil, we consider that there are an estimated 73,610 new cases of breast cancer each year (INCA 2023) [29], and according to data from AMAZONA 3 [24], 40.65 % would be stage II and 54.55 % with a Luminal profile, and according to the AGEMA-BRA study 66.9 % of this population would be aged $\geq$50 years; therefore 14.8 % of these patients could benefit from the use of MammaPrint™, or 10,894 women with breast cancer would be tested, leading to a reduction in chemotherapy for approximately 6,514 patients, 70 % of whom would be treated in the public sector. In a macroeconomic analysis, the potential cost savings could have a significant impact on the allocation of resources for public policies, especially in developing countries, and on the socioeconomic impact more broadly.

## 5. Conclusion

The pharmacoeconomic cost-benefit trial of the MammaPrint™ (70-genes genetic signature) in Brazil showed significant savings in resources when applied to supplementary medicine. In the Unified Health System (SUS), however, with the current prices charged by the platform's distributor, the addition of the genetic signature will generate a significant increase in the individual cost per treatment. Prospects include the need for studies evaluating the cost-effectiveness of the test and an agreement between public and private institutions for the systematic implementation of MammaPrint™ in Brazil.

## Funding

GenCell Pharma.

## Ethics approval

The trial was approved by the institution's Ethics Committee, according to protocol (CAAE) number 12194219.4.0000.0105, technical advice 5.707.195 (Supplementary material – attachment 1).

## Informed consent

Not Applicable.

## Consent to participate

Not applicable.

## CRediT authorship contribution statement

**Fabio Postiglione Mansani:** Writing – original draft, Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Leonardo Ribeiro Soares:** Writing – review & editing, Validation, Formal analysis, Data curation. **Ruffo de Freitas Junior:** Writing – review & editing, Validation, Formal analysis.

## Declaration of competing interest

Fabio Postiglione Mansani – received funding to carry out pharmacoeconomic analysis of MamaPrint™ in the Brazilian population, Leonardo Ribeiro Soares – no conflict of interest, Ruffo de Freitas-Junior – no conflict of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2024.103752.

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