



Budget impact analysis of Oncotype DX[®] multigenic prognostic test in patients with early breast cancer in Italy

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Abstract

Objective This study investigates the mid-term budget impact of using the Oncotype DX[®] multigene prognostic test (MPT) in estrogen receptor (ER)+/ human epidermal growth factor receptor 2 (HER2)- early breast cancer (EBC) patients with 0 to 3 positive lymph nodes, following its recent reimbursement approval in Italy.

Methods A budget impact analysis was conducted from the perspective of the Italian National Health Service (SSN) over a 5-year time horizon. The analysis compared a strategy using MPT to inform chemotherapy (CT) decisions versus standard clinical practice. A hybrid decision-tree and cohort state-transition model was employed, utilizing data primarily from the Italian BONDx study. Sensitivity analyses, including probabilistic and univariate analyses, were performed to assess the robustness of the results and to determine the test price required to offset the budget impact over a five-year time horizon.

Results In the base-case scenario where all ER+/HER2- EBC patients receive the test, MPT use led to a 40.2% reduction in CT prescription. However, the overall budget impact was positive, with an additional cost of €106.1 million (95%CrI 98.5 to 113.6) over five years (approximately €21 million per year), mainly due to the acquisition costs of the MPTs. The maximum cost of the test to have a null budget impact in this scenario was estimated at €560. A scenario where MPTs were only applied to patients with a pre-test CT recommendation based on clinical-pathological criteria showed instead potential annual savings of €5.6 million (–€28.1 million in total, 95%CrI –36.5 to –19.7).

Conclusion Implementing MPTs in ER+/HER2- EBC management in Italy significantly affects CT prescription rates and healthcare expenditures. While MPTs reduce unnecessary CT and related adverse events, their high upfront cost necessitates strategic policy measures to ensure cost-effective implementation. Targeted MPT strategies, focusing on patients with a pre-test chemotherapy recommendation, demonstrate greater efficiency and potential savings for the Italian NHS.

Keywords Multigenic Prognostic Test · Risk score · Budget impact analysis · Early breast cancer, OncotypeDx

Introduction

Breast cancer is the most-commonly diagnosed cancer in Italy in 2024 with 53,686 new cases [1]. Thanks to screening and increased awareness among women, more than 90% of breast malignancies are diagnosed at an early stage when surgical treatment can most often be conservative and the therapy adopted more effective, with a positive impact on survivals. The standard loco-regional treatment of early-stage cancer is conservative surgery combined with radiotherapy or mastectomy. After surgery, adjuvant systemic treatments as hormone-therapy, poly-chemotherapy or molecular-targeted therapy are generally proposed. For the cohort of estrogen receptor (ER)+/human epidermal growth factor receptor 2 (HER2)- patients with lymph nodes at presentation, traditionally pathological and clinical features including patient age,

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ER-status, tumor size, lymph node involvement, histological subtype, grade and Ki67 have traditionally been used to guide treatment decisions; however these parameters are still unable to predict who can safely be spared from chemotherapy [2].

In ER+/HER2-negative early breast cancers (EBC), based on the retrospective data supporting that only a specific proportion of patients benefit from adjuvant chemotherapy [3–5], the genomic prognostic tests have been introduced into the International Guidelines as an additional molecular tools to classify the risk of relapse. These multigenic prognostic tests (MPTs) are based on the analysis of expression of several genes in tissue obtained from the primary tumour after surgical excision or from biopsy samples and can give an indication of the biological aggressiveness of the tumour which, together with the stage of the disease (e.g. size, stage, etc.) and clinical data (e.g. menopausal status), can provide a more complete picture of the evolution of the disease. They have recently become reimbursable by the Italian National Health Service; the Decree of 18 May 2021 of the Ministry of Health has established the distribution modalities and requirements for the use of a fund established for genomic tests for histologically diagnosed early-stage hormone-responsive breast cancer. At least four commercially validated MPTs as Oncotype Dx[®], MammaPrint[®], Endopredict[®], Prosigna[®] are available; they are indicated in patients at intermediate risk of recurrence, for which further definition of the actual usefulness of adding chemotherapy (CT) is therefore necessary of adding adjuvant chemotherapy to endocrine treatment (ET).

The Oncotype DX[®] test is a multigene assay which has been prospectively validated in women with ER+/HER2- breast cancer in the TAILORx (node negative) and RxPONDER (1–3 lymph nodes positive) trials [5–8]. It analyses by Quantitative Real-Time Reverse Transcription PCR (qRT-PCR), the expression of 21 genes on paraffin-embedded histological preparations. Of these 21 genes, 16 are breast cancer-related (including those involved in oestrogen signalling and proliferation) and 5 are control genes. These results are combined in a Recurrence Score[®] (RS) value from 0 to 100, calculated according to a proprietary mathematical algorithm, which reflects underlying tumor biology, with higher scores indicating a worse prognosis and predicting the likelihood of chemotherapy benefit. The test has been also evaluated in international retrospective studies [9–11] and in real-world evaluations in Italy [12, 13].

Furthermore, in patients with ER+/HER2-negative at high risk of recurrence (≥ 4 axillary lymph nodes positive axillary lymph nodes or 1–3 positive axillary lymph nodes with additional high-risk features, such as neoplasm size ≥ 5 cm and/or histological grade 3), the CDK 4/6 inhibitor abemaciclib is reimbursed for 2 years, in combination with adjuvant ET and combined with ovarian suppression in case of pre- or peri-menopausal status [14].

Given the recent approval for reimbursement of MPTs in Italy, the objectives of this study were to investigate the mid-term economic impact of Oncotype Dx[®], largely used in Italian ER+/HER2- breast cancer patients with lymph node negative (N0) or 1–3 positive lymph nodes.

Methods

Target population

The target population for this analysis consists of patients with EBC (stages I–IIIa) who ER+/HER2- with 0 to 3 positive lymph nodes. We have integrated these characteristics with the criteria exposed into the Italian Decree [15], which restricts the access to MPT to patients classified as intermediate-risk based on clinical-pathological features derived from the St. Gallen Consensus Guidelines (i.e., combining nuclear grade, tumour size, Ki67, nodal involvement and ER level) [16]. Our analysis relies primarily on prospective data gathered and published as part of the Italian BONDx study based on Oncotype DX[®] test [17]. In absolute numbers, this target population corresponds to approximately 14,800 women per year, of whom 67% are node-negative and 33% have one to three positive lymph nodes.

Intervention

Multigene expression profiling when used in addition to clinical-pathological factors has revolutionised the adjuvant treatment of ER+/HER2- EBC [18–20]. In our analysis, we consider the Oncotype Dx[®] assay.

Comparator

The use of MPTs as a decision support tool to inform decisions to administer CT (MPT strategy) was compared to current clinical practice in Italy (standard of care - SOC strategy) which includes consideration of clinical and pathological characteristics, as well as any risk quantification tools, and discussions within multidisciplinary teams.

Model structure

The analysis takes the perspective of the Italian National Health Service (SSN) and evaluates the budgetary impact of adopting MPTs (Oncotype Dx[®]) in early-stage breast cancer over a 5-year time horizon. The model structure is similar to those used in previous analyses [21, 22] and is based on a

hybrid decision-tree plus a cohort state-transition model. The decision-tree component classifies patients in both groups (SOC strategy and MPT strategy) into high, medium, and low-risk categories based on the recurrence score (RS) from the test. The cut-off thresholds for classification are < 10 for low risk, between 11 and 25 for intermediate risk, and ≥ 26 for high risk of recurrence. The treatment group (MPT or SOC) and the risk level determined by the test then define the probability that the patient will subsequently receive adjuvant chemotherapy. With both the MPT strategy and the SOC strategy, the decision tree determines the likelihood that a patient will be assigned to one of six groups: [1] low risk, chemotherapy; [2] low risk, no chemotherapy; [3] intermediate risk, chemotherapy; [4] intermediate risk, no chemotherapy; [5] high risk, chemotherapy; and [6] high risk, no chemotherapy. Each branch is then connected to a cohort state-transition model that predicts patient costs based on the patient's risk of distant recurrence and whether they receive chemotherapy. Figure 1 graphically illustrates the decision tree and cohort state-transition model structures.

Each state, in the state transition model, is evaluated over 10 cycles of 6 months, equivalent to 5 years in total. The model includes three health states: [1] recurrence-free [2], distant recurrence, and [3] death. For all Markov nodes, patients enter the model in the recurrence-free state. During each 6-month cycle, patients who are recurrence-free can remain in their current health state, develop distant recurrence, or die. Patients with distant recurrence can either remain in their current health state or die. Patients may die from breast cancer or other causes, according to general population mortality data published by the Italian National Institute of Statistics (ISTAT) (supplementary tables S1 and S2).

The benefits of additional chemotherapy were estimated using a relative risk of developing distant recurrence in each risk category defined by the MPT. The impact of the MPT is therefore captured in the model solely based on its prognostic benefit, i.e., by changing the probability that patients in each risk category, as defined by the MPT, will receive adjuvant chemotherapy. However, the model does not consider the predictive benefit of the MPT regarding the effectiveness of chemotherapy based on the patient's RS. For this reason, the relative risk parameter for the protective effects of adjuvant chemotherapy, compared to ET alone, is assumed to be equal across the different risk categories.

Model parameters

The full list of parameters values used in the model is provided in the supplementary material and briefly described below.

Clinical and epidemiological parameters

Treatment patterns, i.e., whether ET alone or ET + CT, with and without genomic risk assessment were derived from the observational prospective study BondX [17]. The study examines therapeutic recommendations with and without genomic risk assessment in a sample of 394 patients treated at four centers in Lombardy Region, Italy. The study estimated a 38% reduction in CT prescription, from 24.6% without MPT to 14.7% with MPT (49 changes in treatment decisions from ET + CT to ET alone). The study also observed 12 changes in treatment recommendations from ET alone, to ET + CT, in patients with high RS score registered.

The impact of MPT on reducing chemotherapy prescriptions is strongly influenced by the choice of test cut-off thresholds, which guide treatment decisions. Initial studies on Oncotype Dx® categorized patients as low risk ($RS < 18$) or high risk ($RS \geq 31$) for recurrence. However, subsequent research, particularly the TAILORx study (for N0 patients) and the RxPONDER study [6] (for N1 patients), used different thresholds that have reshaped post-MPT treatment recommendations. Both studies found no significant benefit from adjuvant chemotherapy in postmenopausal patients (aged > 50) with $RS \leq 25$. However, they observed a potential benefit of chemotherapy in premenopausal women, though this finding remains debated due to the possible confounding effects of ovarian suppression and variations in the quality of ET. Consequently, uncertainty persists regarding the optimal treatment approach for premenopausal N0 patients with RS between 16 and 25, whereas for N1 patients, chemotherapy is typically recommended unless ovarian suppression combined with ET offers equivalent benefits. Studies on pre- and post-MPT treatment recommendations in Italy, including BondX, were conducted before this new evidence became available. To incorporate the impact of this updated evidence, we assumed that all post-menopausal patients would receive ET alone for $RS \leq 25$ or ET + CT for $RS > 25$, whereas for premenopausal patients, treatment recommendations followed the original recommendations stated in the BondX study, i.e. 33% of 108 premenopausal women were recommended for CT before knowing about the outcome of the test.

Transition probabilities from the recurrence-free to distant recurrence were RS- and treatment-specific (supplementary table S3). Transition probability of developing distant recurrence by RS with endocrine therapy alone was derived for node-negative patients from the TAILORx [5] and NSABP B-20 [23] studies and was assumed to be the same for node positive patients conditional on their RS. The cycle probability of developing distant recurrence was calculated using 10-year risk of recurrence and assuming

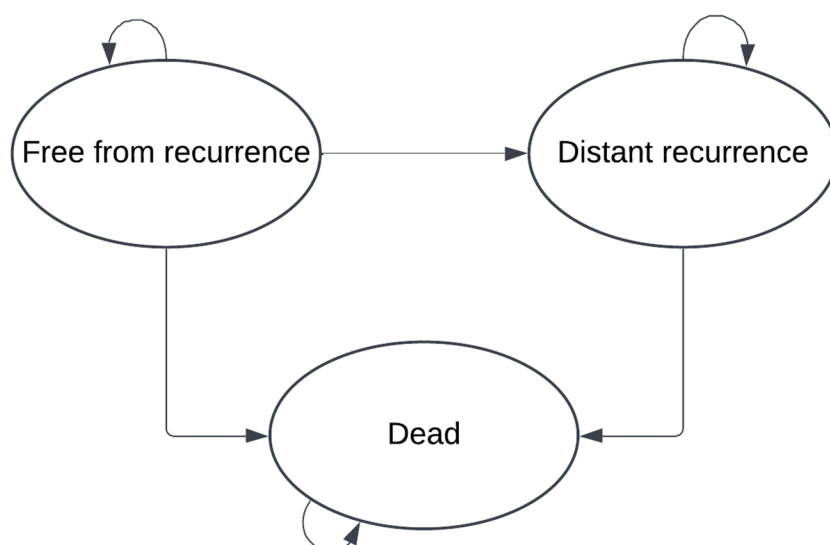
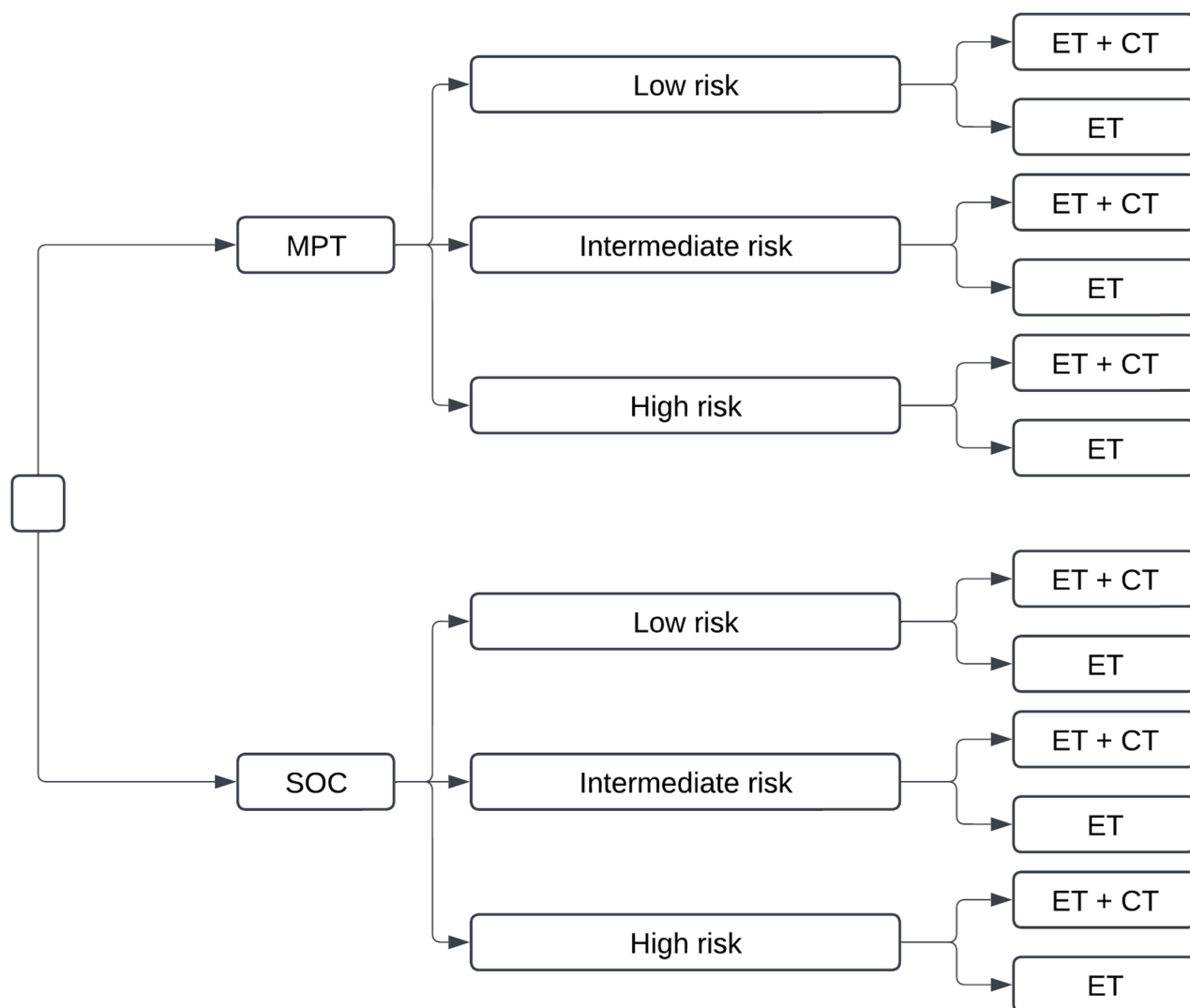


Fig. 1 Decision-tree and cohort state-transition model structure of the budget impact analysis. MPT: Multigenic Prognostic Test group; SOC: Standard of care group; ET: Endocrine Therapy; CT: Chemotherapy

a constant hazard over time. The model also assumed that about 10.5% of patients developing a distant recurrence, previously experienced a local recurrence, based on the study from De Bock et al. [24]. The additional benefit of the CDK4/6 inhibitor ribociclib, in combination with ET, was modelled for a proportion of patients in both the SOC and MPT groups. In the SOC group, ribociclib was administered to patients with tumors classified as AJCC anatomical stage IIA or higher. T2N0 tumors were eligible for ribociclib only if classified as Grade 3 or Grade 2 with Ki67 $\geq$ 20%. In the MPT group, ribociclib eligibility included the same criteria as the SOC group but was expanded to include all patients with an RS $>$ 25. The proportions of patients eligible for ribociclib were derived from the BondX study, and were similar in the MPT group (43.4%) and in the SOC group (43.1%). The distribution across treatment regimens with and without genomic risk assessment is reported in supplementary table S4. The hazard ratio of distant recurrence with ribociclib in combination with ET compared to ET alone was derived from the NATALEE study [25] and estimated at 0.74 (95% CI 0.91; 0.6).

The protective effect of CT on the probability of developing distant recurrence was estimated at 0.69 (standard error 0.04) based on a meta-analysis from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [26].

In 2023, the incidence of breast cancer in the female population of Italy was estimated at 55,300 new cases with an expected annual growth rate of 0.2% over the next 5 years [1]. Based on the ratio of patients excluded and included in the BondX study, it was estimated that 27% of the incident population (394 patients included in the study out of 1482 consecutively evaluated patients) would be recommended for MPT, i.e., had breast cancer diagnosed at stages T1-T3, with HR-positive, HER2-negative tumors, positive lymph nodes (from 0 to 3), and an intermediate clinical-pathological risk assessment. Of these patients, 67% had tumors with negative lymph nodes (N0), while 33% had tumors with positive lymph nodes (N1-N3) (supplementary table S5).

Economic parameters

The model accounted for the costs associated with the following elements: the cost of the MPT; the costs related to CT, including the management of toxicity, central venous catheter placement, diagnostic tests, and supportive therapies; the costs associated with ET, including the cost of CDK4/6 inhibitor in selected patients; and the costs of treating localized recurrences and distant metastases. Treatment

costs for long-term adverse event were not included, as these events (e.g., leukemias or myelodysplastic syndromes) were considered extremely rare (0.2% of cases) and have minimal impact on overall costs in the short term [27]. A detailed description of the approach used to calculate patient costs is provided in the supplementary table S6. The cost of the MPT was derived from Regional Decree No. XI/1986 issued by Lombardy Region, and estimated at €2,000. Drug costs, including ET drugs, CT drugs, Target Therapy (ribociclib) and support therapies (e.g., pegfilgrastim) were derived from the hospital pharmacy department of one hospital in Italy, or from public prices published by the Italian Medicines Agency (AIFA). Costs of complications related to CT as well as other services related to treatments (e.g., placement of central venous catheter, or mastectomy following local recurrence) were derived from national or regional tariffs.

Scenario and sensitivity analyses

In the base-case scenario, MPT was offered to all ER+/HER2- patients with early-stage breast cancer (stages I-IIIa) N0 to N3 regardless of the initial recommendation based on clinical-pathological criteria. In the BondX study, 12 out of 394 (3%) patients switched from ET alone to ET+CT after genomic risk assessment, indicating that a minor proportion of patients may go undertreated in the absence of genomic assessment. However, a second scenario considered offering MPT only to patients who had a CT recommendation based solely on clinical-pathological criteria. Treatment approaches for patients initially recommended for ET remained unchanged. The budget impact estimates for the MPT on current clinical practice are based on expected average values for clinical and economic parameters. Uncertainty in these model parameters was assessed using probabilistic sensitivity analysis (PSA), which involved generating 5000 Monte Carlo simulations. Each model parameter was assigned a probability distribution based on available data. In the model, Beta or Dirichlet distributions were used for probability parameters (binomial or multinomial), log-normal distributions for relative risk parameters, and Gamma distributions for cost parameters. For costs derived from DRG rates, a standard error of 20% of the mean value was assumed for all values. Finally, a deterministic one-way sensitivity analysis was conducted to estimate the maximum price of the MPT at which the 5-year budget impact would be zero as compared to the standard of care.

In addition, two univariate sensitivity analyses were conducted in the base case. The first examined how the budget impact was influenced by the pre-test propensity to prescribe

CT, while the second assessed how variations in the cost of the MPT affected the budget impact.

Results

In the base case scenario, 24.6% patients, approximately 3640 women per year, received CT with the SOC, while only 14.7% patients (approximately 2175 women per year) received CT with MPTs, corresponding to a 40.2% reduction in CT prescription. Accordingly, the average cost per patient for chemotherapy was €837 (95% CrI 599; 1,128) for patients undergoing MPT and €1,397 (95% CrI 1,040; 1,872) for patients who did not receive this test. Overall, the budget impact per patient was €1,434 (95% CrI 1,235; 1,771) (Fig. 2).

The total cost of CT and the total budget impact for all ER+/HER2- patients with EBC, regardless of the initial recommendation based on clinical-pathological criteria, are reported in Table 1. In the base-case scenario without MPT, the 5-years mean annual chemotherapy costs was €20.7 million, of which about 10% are dedicated to the management of adverse events (i.e., €2.5 million per year). The estimated cost for ET and for treatment of local and distant

recurrences was €69.8 million per year and €5.3 million per year, respectively. Over the 5-year period the total estimated cost to treat the relevant population is €479 million (95% CrI €444 million; 672 million). In the base-case scenario with MPT, the mean annual chemotherapy costs were €12.4 million per year, with €1.5 million dedicated to the management of adverse events. The estimated cost for endocrine therapy and for treatment of local and distant recurrences are similar compared to the SOC approach, i.e. €69.9 million per year and €5.1 million per year, respectively. However, the acquisition of the MPTs amounted to €29.5 million per year, that is €148 million in total for the 5-year period. The total estimated cost to treat the relevant population using MPTs is €585 million. Cumulatively, the estimated budget impact is positive, with a total extra €106 million expenditure, that is about €21 million per year, due to MPTs cost not offset by annual savings in chemotherapy (€8.3 million).

Scenario and sensitivity analyses

The sensitivity analysis on the proportion of patients with a pre-test recommendation for CT showed that a null budget impact would require 50% of patients to have a pre-test CT

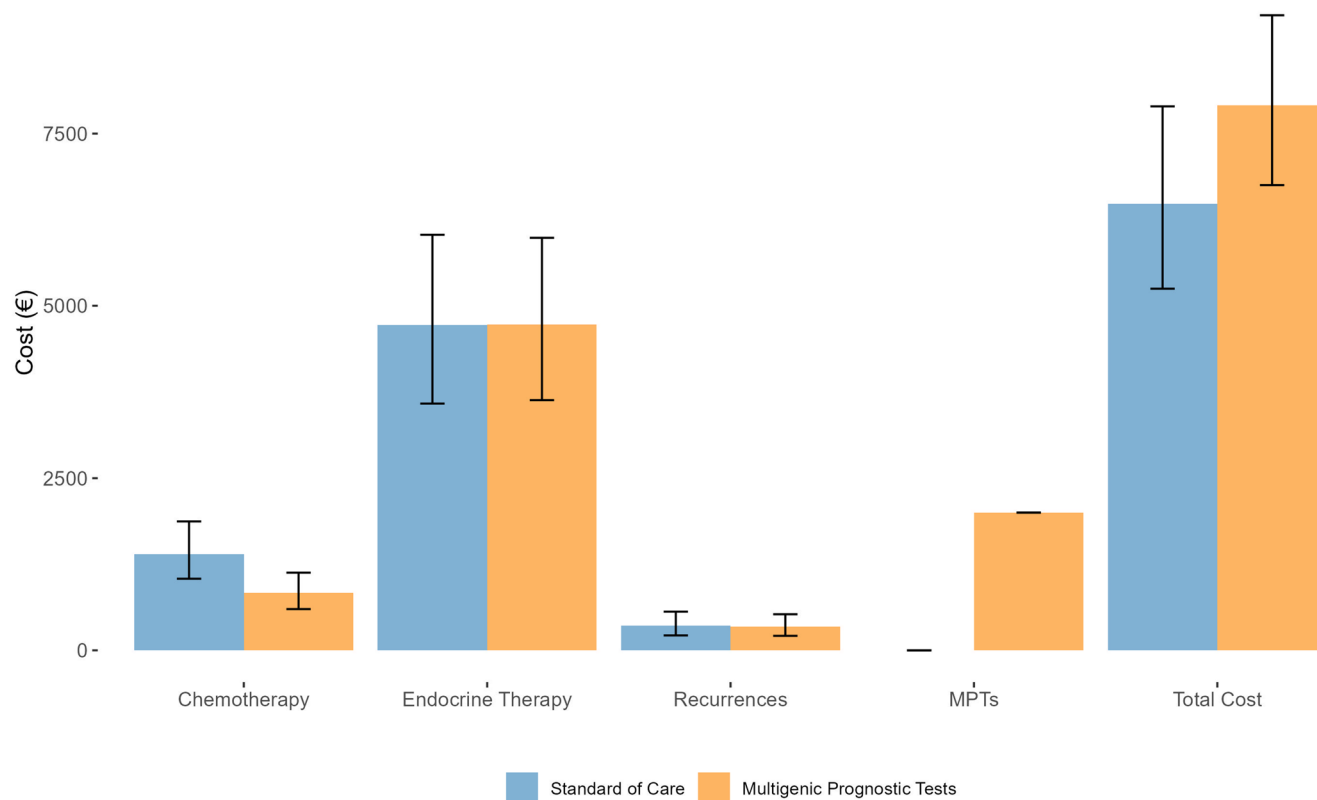


Fig. 2 Budget impact per patient with and without the MPT by type of costs

Table 1 Budget impact related to the introduction of MPT in all ER+/HER2- patients with early-stage breast cancer N0 to N3 over 5 year - Million € (95% Credible Interval)

Standard of Care						
	2024	2025	2026	2027	2028	5-years total
Chemotherapy	20.6 (15.3; 27.6)	20.6 (15.3; 27.6)	20.7 (15.4; 27.7)	20.7 (15.4; 27.7)	20.7 (15.4; 27.8)	103.3 (97.7; 108.9)
of which Management costs for adverse events	2.5 (1.8; 3.3)	2.5 (1.8; 3.3)	2.5 (1.8; 3.3)	2.5 (1.8; 3.3)	2.5 (1.8; 3.3)	12.3 (10.4; 14.2)
Endocrine Therapy	69.5 (52.7; 88.8)	69.7 (52.8; 89)	69.8 (52.9; 89.2)	69.9 (53; 89.4)	70.1 (53.1; 89.5)	349 (339.4; 358.6)
Local and distant recurrence	5.3 (3.2; 8.3)	5.3 (3.2; 8.3)	5.3 (3.2; 8.3)	5.3 (3.2; 8.3)	5.4 (3.2; 8.3)	26.7 (23.1; 30.3)
Multigenic prognostic tests	0	0	0	0	0	0
Total	95.4 (71.2; 124.7)	95.6 (71.4; 124.9)	95.8 (71.5; 125.2)	96 (71.7; 125.4)	96.2 (71.8; 125.7)	479 (467.3; 490.7)
Multigenic Prognostic Test						
	2024	2025	2026	2027	2028	5-years total
Chemotherapy	12.3 (8.8; 16.6)	12.4 (8.8; 16.6)	12.4 (8.9; 16.7)	12.4 (8.9; 16.7)	12.4 (8.9; 16.7)	61.9 (57.4; 66.4)
of which Management costs for adverse events	1.5 (1.1; 2)	1.5 (1.1; 2)	1.5 (1.1; 2)	1.5 (1.1; 2)	1.5 (1.1; 2)	7.4 (5.8; 8.9)
Endocrine Therapy	69.7 (53.5; 88.2)	69.8 (53.6; 88.4)	69.9 (53.7; 88.5)	70.1 (53.8; 88.7)	70.2 (53.9; 88.9)	349.7 (340.3; 359.1)
Local and distant recurrence	5.1 (3.1; 8.3)	5.1 (3.1; 7.7)	5.1 (3.1; 7.8)	5.1 (3.1; 7.8)	5.1 (3.1; 7.8)	25.6 (22.1; 29.1)
Multigenic prognostic tests	29.5	29.5	29.6	29.6	29.7	148.0
Total	116.6 (94.8; 142.5)	116.8 (95; 142.3)	117 (95.2; 142.6)	117.3 (95.4; 142.8)	117.5 (95.6; 143.1)	585.1 (574.1; 596.1)
Budget Impact						
	2024	2025	2026	2027	2028	5-years total
Total	21.1 (7; 35.2)	21.2 (7.1; 35.2)	21.2 (7.1; 35.3)	21.3 (7.2; 35.3)	21.3 (7.2; 35.4)	106.1 (98.5; 113.6)
of which						
Chemotherapy	-8.3 (2; 14.5)	-8.3 (2; 14.5)	-8.3 (2; 14.6)	-8.3 (2; 14.6)	-8.3 (2; 14.6)	-41.4 (36.4; 46.5)
Multigenic Prognostic Tests	29.5	29.5	29.6	29.6	29.7	148.0

recommendation. The pre-test proportion of patients recommended for CT is similar to the one measured in the Roxane study (i.e., 52%) [12]. As for the cost of the MPT, the max cost of the test to have a null budget impact in the base case scenario was estimated at €560 (Fig. 3).

In a scenario analysis, we considered to implement MPTs only with ER+/HER2- patients with early-stage breast cancer who had a chemotherapy recommendation based solely on clinical-pathological criteria. In this scenario, a fewer proportion of patients received chemotherapy (8.9%), mostly due to the fact that post-menopausal patients with RS>25 and a pre-test recommendation for ET would not switch to CT in this scenario (Fig. 4). Overall, the reduction in CT prescription compared to the SOC was estimated at 63.9% in this scenario.

The results of the budget impact analysis are illustrated in Table 2. Compared to the base-case scenario, the budget impact in this case is negative, due to lower cost for MPTs acquisition (€7.3 million per year on average) and higher annual savings in CT (about €13.1 million per year). Overall, optimizing the target population for the genomic testing would produce €5.6 million savings yearly, or €28.1 million over 5-year.

Discussion

The implementation of MPTs in the management of ER+/HER2- EBC significantly affects CT prescription rates and overall healthcare expenditures. In the base-case scenario of our analysis, MPTs, focused on all HR+/HER2- EBC with lymph node negative (N0) or 1–3 positive lymph nodes in Italy, led to a 40.2% reduction in CT use, decreasing from 24.6% in the SOC approach to 14.7% in the MPT-guided approach. This reduction translated into lower chemotherapy-related costs, with an average per-patient expenditure of €~840 for MPT-tested patients compared to €~1,400 for those who did not undergo testing. However, despite annual chemotherapy savings of €8.0 million, the overall budget impact remained positive, with an additional cost of €105 million over five years (~€21 million per year), primarily driven by MPT acquisition costs (€147.5 million over five years or €29.5 million per year). It is worth noting that the additional costs are not due to more women treated with the CDK4/6 inhibitor ribociclib, as the proportions of patients eligible for this targeted drug are similar in the two scenarios with and without MPT (only 0.3% of extra treated patients in the MPT group). Based on our sensitivity analysis, a

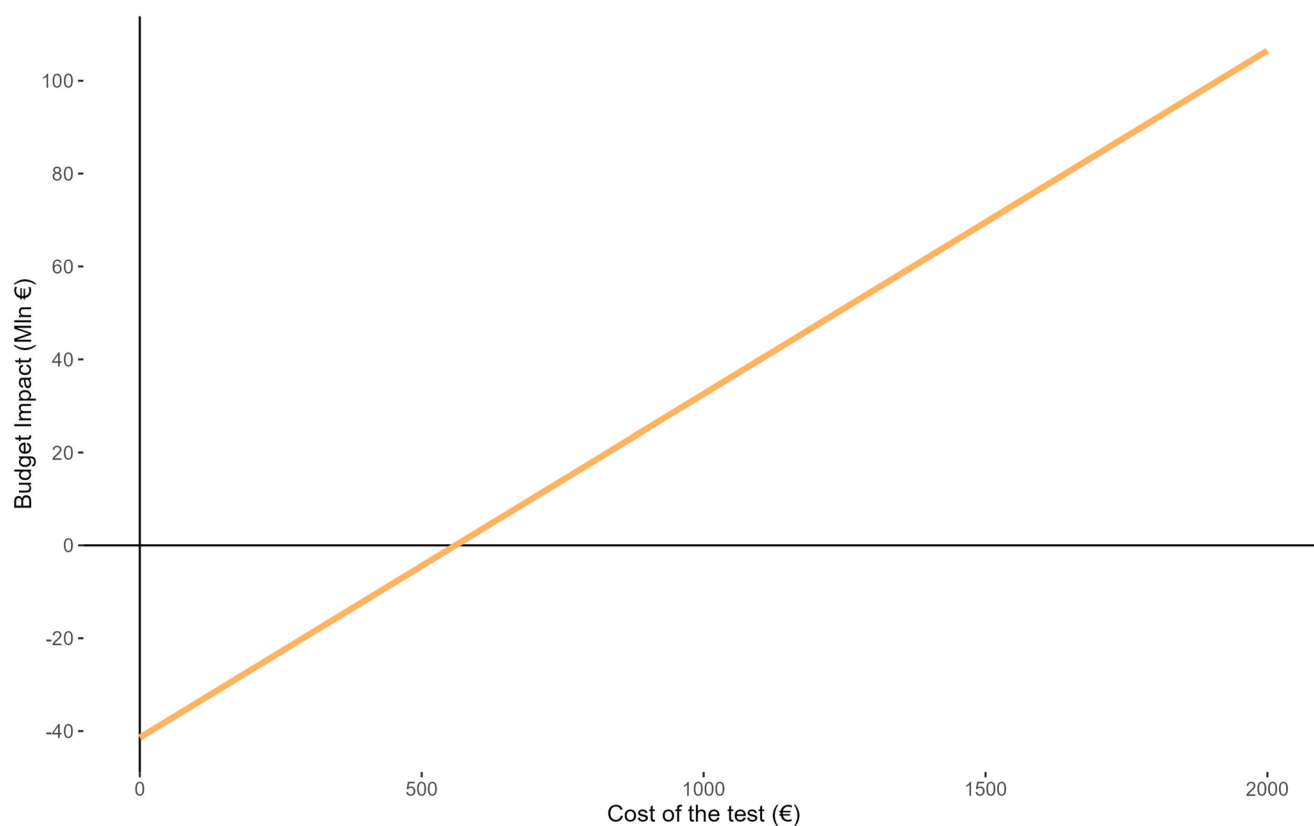


Fig. 3 Variations in the budget impact at different costs of the multigenic prognostic test

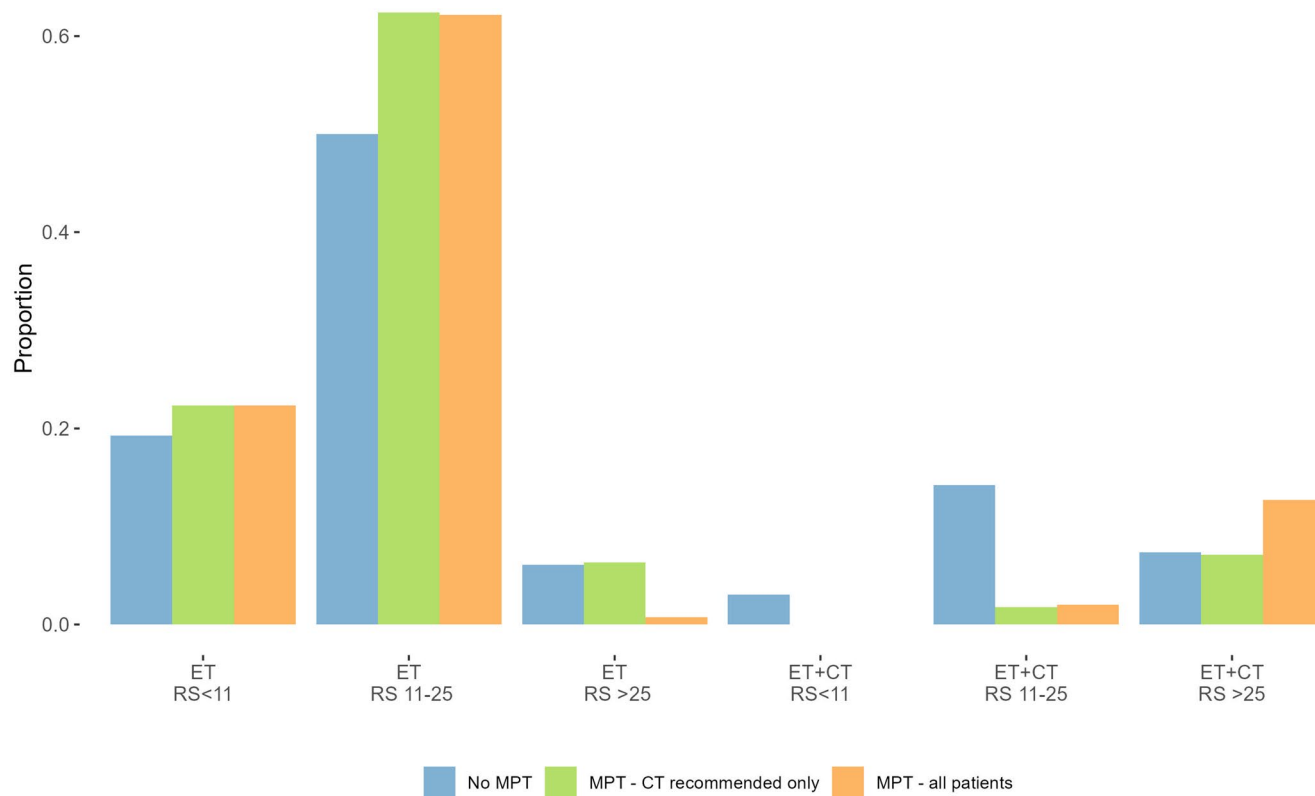


Fig. 4 Treatment recommendations across risk scores and scenarios

Table 2 Budget impact related to the introduction of MPT in ER+/HER2- patients with early-stage breast cancer N0 to N3 who had a chemotherapy recommendation based solely on clinical-pathological criteria over 5 year (Million €)

Standard of Care						
	2024	2025	2026	2027	2028	5-years total
Chemotherapy	20.5 (14.8; 26.8)	20.5 (14.8; 26.9)	20.6 (14.9; 27)	20.6 (14.9; 27)	20.7 (14.9; 27.1)	102.9 (97.3; 108.4)
of which Management costs for adverse events	2.4 (1.8; 3.2)	2.4 (1.8; 3.2)	2.5 (1.8; 3.2)	2.5 (1.8; 3.2)	2.5 (1.8; 3.2)	12.3 (10.3; 14.2)
Endocrine Therapy	69.3 (52.9; 88.2)	69.5 (53; 88.4)	69.6 (53.1; 88.5)	69.7 (53.2; 88.7)	69.9 (53.3; 88.9)	348 (338.5; 357.5)
Local and distant recurrence	5.3 (3.3; 8.2)	5.4 (3.3; 8.2)	5.4 (3.3; 8.3)	5.4 (3.3; 8.3)	5.4 (3.3; 8.3)	26.8 (23.3; 30.4)
Multigenic prognostic tests	0	0	0	0	0	0
Total	95.2 (71; 123.2)	95.4 (71.1; 123.5)	95.5 (71.3; 123.7)	95.7 (71.4; 124)	95.9 (71.6; 124.2)	477.7 (466.1; 489.3)
Multigenic Prognostic Test						
	2024	2025	2026	2027	2028	5-years total
Chemotherapy	7.4 (4.8; 10.7)	7.4 (4.9; 10.7)	7.4 (4.9; 10.7)	7.4 (4.9; 10.7)	7.5 (4.9; 10.7)	37.1 (33.3; 41)
of which Management costs for adverse events	0.9 (0.6; 1.3)	0.9 (0.6; 1.3)	0.9 (0.6; 1.3)	0.9 (0.6; 1.3)	0.9 (0.6; 1.3)	4.4 (3.1; 5.8)
Endocrine Therapy	69.4 (52.9; 87.4)	69.6 (53; 87.6)	69.7 (53.1; 87.8)	69.8 (53.2; 87.9)	70 (53.3; 88.1)	348.5 (339.1; 357.9)
Local and distant recurrence	5.5 (3.4; 8.2)	5.5 (3.4; 8.4)	5.5 (3.4; 8.4)	5.5 (3.4; 8.5)	5.6 (3.4; 8.5)	27.7 (24.1; 31.2)
Multigenic prognostic tests	7.2	7.3	7.3	7.3	7.3	36.4
Total	89.6 (68.4; 113.5)	89.8 (68.5; 113.9)	89.9 (68.7; 114.2)	90.1 (68.8; 114.4)	90.3 (68.9; 114.6)	449.6 (438.9; 460.4)
Budget Impact						
	2024	2025	2026	2027	2028	5-years total
Total	-5.6 (-19.4; 8.2)	-5.6 (-19.4; 8.2)	-5.6 (-19.5; 8.2)	-5.6 (-19.5; 8.2)	-5.6 (-19.5; 8.3)	-28.1 (-36.5; -19.7)
of which						
Chemotherapy	-13.1 (-19; -7.2)	-13.1 (-19; -7.2)	-13.1 (-19.1; -7.2)	-13.2 (-19.1; -7.2)	-13.2 (-19.1; -7.3)	-65.7 (-71.2; -60.2)
Multigenic Prognostic Tests	7.2	7.3	7.3	7.3	7.3	36.4

maximum cost of €560 for the MPT would cancel out the budget impact at 5 year, and this value corresponds to 28% of the MPT cost considered in our model (i.e., €2000).

The budget impact is instead expected to be negative if the MPTs were only given to women who had a recommendation to receive chemotherapy based on clinical-pathological criteria, with annual savings under this scenario of €5.6 million. Whilst beneficial from a financial point of view, this choice needs to account for the concrete, albeit low (e.g. 3% or slightly more, 9%, as reported in TAILORx), risk of undertreatment for patients who could have received adjuvant CT in combination with hormone therapy – starting from a hormone therapy recommendation alone – following MPT administration.

One limitation of this evaluation is that many parameters are derived from the Lombardy BONDx study, for which patient-level data were available. Although its representativeness of patients and clinical practice across all Italian regions may be somewhat limited, the BONDx cohort comprised a consecutive and unselected population of 394 early breast cancer patients treated in four large general hospitals in Lombardy. This represents the largest prospective study conducted in Italy to date evaluating the 21-gene test in

ER+/HER2-early breast cancer patients with intermediate risk of relapse, as defined by clinical-pathologic factors commonly used nationwide.

Another limitation is the application of TAILORx risk-based recurrence rates to N1-3 patients since this parameter was not directly available from the RxPONDER study. Future models should incorporate more granular genomic-clinical risk estimates stratified recurrence rates, as more mature N+ data become available.

The proportion of patients with a pre-test recommendation for CT affects our results. We found that a 50% proportion of patients with a pre-test recommendation for CT would zero the budget impact, and this value is comparable to what was reported in the Roxane study, although this study recruited N0–N1 EBC patients [12] to show a statistically significant 16% net reduction in the proportion of patients with a recommendation to CT from pre-RS (52%) to post-RS (36%).

In this analysis we refer generically to MPTs, however the data considered refer to the Oncotype Dx® test only. An extension of this work could concern other tests currently on the market, for which, however, robust studies representative of the Italian reality are not available. Lux and

colleagues have compared the economic profile of different gene expression tests (i.e., Oncotype Dx[®], EndoPredict[®], MammaPrint[®], Prosigna[®]) to conclude that Oncotype Dx[®] test led to higher estimated average savings per patient compared to the other tests [28, 29]. However, these studies were sponsored by the test manufacturer. More recently, a budget impact analysis in Brazil found that widespread use of the MPT could yield substantial cost savings (\$19.3–\$26.7 million USD) by optimizing chemotherapy recommendations and reducing overtreatment in most patient subgroups. However, younger low-risk node-negative patients and premenopausal node-positive patients showed increased costs, highlighting nuanced economic impacts across clinical subpopulations [30].

The unit cost values for outpatient and surgical services considered refer to the Lombardy Region context, but the sensitivity analysis in which each value is modified does not produce significant differences. In addition, the analysis assumes a test delivery to 100% of eligible patients, in this sense our results can be considered conservative.

In 2020, Health Quality Ontario, released a health technology assessment report for the Canadian province. In a budget impact analysis they estimated additional costs of \$1.29 million in year 1, up to \$2.22 million in year 5, for a total cost increase of \$8.13 million [31]. This is assuming that initially 80% of eligible patients receive the test at year 1, increasing progressively to 100% at year 5. MPTs are considered likely cost-effective compared with no testing in both lymph-node negative and lymph-node positive populations. A German study, however, reported savings associated with the use of Oncotype Dx[®] of €4,272 per node-positive patient [32]. The greatest savings resulted from reductions in direct treatment costs and costs arising from the treatment of chemotherapy-related side effects (about €6.677) and slightly lower costs for treatment of distant metastasis. An Irish national evaluation has recently reported net savings of over €3.3 million between 2011 and 2022 post Oncotype Dx[®] assay use in ER+/HER2- breast cancer patients and a 58% reduction in chemotherapy administration [33].

Given the budgetary implications of MPTs, policymakers should consider evidence-based strategies to optimize their integration into healthcare systems as (1) Risk-Stratified Reimbursement Models, instead of universal reimbursement, selective funding for high-risk patient groups (e.g., those with a clinical-pathological indication for chemotherapy) can maximize cost-effectiveness while reducing unnecessary testing; (2) A targeted MPT strategy, preferred in our scenario analysis, which reduces CT by 63.9% and generates annual net savings of €5.6 million (€28 million over five years), reinforcing the financial sustainability of a risk-adapted reimbursement approach.

Countries with centralized HTA agencies should incorporate real-world cost-effectiveness data into reimbursement frameworks. Long-term outcomes, such as recurrence rates, survival benefits, and quality-adjusted life years (QALYs), should guide policy decisions rather than focusing solely on short-term budget impacts.

Conclusions

The use of economic evidence to inform health policy decisions should be encouraged to promote the efficiency of decisions that are relevant to the whole NHS. This analysis of the impact on Italian NHS budgets of MPTs in breast cancer suggests a net increase in expenditure over the next 5 years of more than €20 million per year in case the indication for MPT is not optimized. To achieve savings in the NHS of about €5.6 million yearly in the med-term as a result of the introduction of MPT, the criteria for accessibility to the test should consider ex-ante indication for chemotherapy based on clinical and pathological evaluation.

A targeted scenario analysis, in which MPTs were used only in patients with a pre-test chemotherapy recommendation based on clinical-pathological criteria, demonstrated greater efficiency. These findings highlight the clinical and economic implications of integrating MPTs into routine oncology practice. While MPTs reduce unnecessary CT, whilst improving patient quality of life and minimizing toxicity-related complications, their high upfront cost necessitates strategic policy measures to ensure cost-effective implementation.

In our opinion, Real-World Evidence (RWE) databases and genomic registries should be leveraged to track MPT utilization, measure clinical effectiveness, and refine reimbursement decisions dynamically.

Future research should focus on: (1) long-term survival benefits and real-world cost-effectiveness of MPTs; (2) further evaluation of treatment de-escalation strategies, assessing whether broader adoption could yield greater healthcare efficiencies; (3) cross-border collaboration and data-sharing initiatives to harmonize reimbursement frameworks and optimize genomic-driven treatment strategies globally.

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Data availability The parameters are available in the Supplementary material. The budget impact model is available from the authors upon request.

Declarations

Ethical statement This study did not require ethical approval from the Ethical Review Committee at Bocconi University. This article is based on previously collected aggregate or anonymised data.

Conflict of interest D.G. has received honoraria from Novartis, Lilly, AstraZeneca, Roche, Pfizer, and Menarini; research funding from Novartis; and travel/accommodation support from Novartis, Roche, and Pfizer. A.Z. has received honoraria and/or consulting fees from Eli Lilly, Novartis, and Roche/Genentech. He has also received travel, accommodations, and/or meeting support from the same companies. O.C. and C.F. declare no conflict of interest.

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