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Original Article

Prospective budget impact analysis of the rt-PCR test to identify EGFR gene mutations in patients with non-small cell lung cancer

Análise de impacto orçamentário prospectivo do teste rt-PCR para identificação de mutação do gene EGFR em pacientes com câncer de pulmão de células não pequenas

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ABSTRACT

Objective: to estimate the budgetary impact of incorporating the rt-PCR test for identifying EGFR mutations in patients with non-small cell lung cancer (NSCLC) into the Brazilian Unified Health System (SUS). **Method:** deterministic modeling was carried out, considering a 5-year time horizon (2023-2027). The eligible population was estimated based on the analysis of the demand of the measured population diagnosed with advanced or metastatic NSCLC and treated with chemotherapy in the SUS between 2015-2021. The data was obtained from the Outpatient Information System (SIA-SUS) database. Only the direct cost of the rt-PCR test was considered in the calculation. A technology diffusion rate was estimated in two scenarios. The uncertainties attributed to the model were tested in the sensitivity analysis, applying a variation of plus or minus 25%. **Results:** between 2015-2021, 40,857 individuals with NSCLC were treated with chemotherapy in the SUS. The population eligible to undergo rt-PCR testing in the 2023-2027 period was estimated at 31,918 individuals. The budgetary impact of a possible adoption of the technology was R$ 23,186,140.03 in alternative scenario 1, and R$ 38,301,950.72 in alternative scenario 2. The sensitivity analysis estimated an incremental budget of R$ 17,389,605.03 for the best scenario and R$ 47,877,438.40 for the worst. **Conclusion:** the analysis showed that incorporating the rt-PCR test could be feasible for the health system, favoring the rational use of the tyrosine kinase inhibitors erlotinib and gefitinib. Keywords: Budget Impact Analysis of Therapeutic Advances; Epidermal Growth Factor Receptor Coding Genes; Lung Cancer; Unified Health System.
Keywords: Budget Impact Analysis of Therapeutic Advances; Epidermal Growth Factor Recep-tor Coding Genes; Lung Cancer; Unified Health System

RESUMO

Objetivo: estimar o impacto orçamentário com a incorporação do teste rt-PCR para identificação da mutação no EGFR em pacientes com câncer de pulmão de células não pequenas (CPCNP) no Sistema Único de Saúde (SUS). **Método:** foi realizada uma modelagem determinística, considerando um horizonte temporal de 5 anos (2023-2027). A população elegível foi estimada com base na análise da demanda de população aferida diagnosticada com CPCNP avançado ou metastático, e tratada com quimioterapia no SUS, entre 2015-2021. Os dados foram obtidos da base de dados do Sistema de Informação Ambulatorial (SIA-SUS). Considerou-se no cálculo apenas o custo direto do teste rt-PCR. Estimou-se uma taxa de difusão da tecnologia em dois cenários. As incertezas atribuídas ao modelo foram testadas na análise de sensibilidade, aplicando-se variação de 25% para mais e para menos. Resultados: entre 2015-2021, 40.857 indivíduos com CPCNP foram tratados com quimioterapia no SUS. A população elegível a ser submetida ao teste de rt-PCR, no período de 2023-2027, foi estimada em 31.918 indivíduos. O impacto orçamentário acumulado em cinco anos de uma possível adoção da tecnologia foi de R$ 23.186.140,03 no cenário alternativo 1, e de R$ 38.301.950,72 no cenário alternativo 2. Na análise de sensibilidade estimou-se um orçamento incremental de R$ 17.389.605,03 para o melhor cenário e de R$ 47.877.438,40 para o pior. **Conclusão:** A análise demonstrou que a incorporação do teste rt-PCR pode ser factível ao sistema de saúde, favorecendo o uso racional dos inibidores de tirosina quinase erlotinibe e gefitinibe.
Palavras-chave: Análise de Impacto Orçamentário de Avanços Terapêuticos; Genes Codificadores dos Receptores de Fator de Crescimento Epidérmico; Câncer de Pulmão; Sistema Único de Saúde

Introduction

Lung cancer (LC) is the second most commonly diagnosed neoplasm in the world, with 2.2 million cases (11.4%) reported in 2020, making it the neoplasm with the highest mortality rate (18%).[1] In Brazil, according to the 2023 estimates from the National Cancer Institute (INCA), lung cancer accounts for the third most common neoplasm in men, with 18,020 cases (7.5%), and the fourth most common in women, with 14,540 cases (6.0%).[2]

Lung cancer exhibits a diverse etiology, with two main histological types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), comprising 15% and 85% of lung cancers, respectively.[3] The majority of patients are diagnosed at an advanced stage (IIIB) and/or metastatic stage (IV) due to late diagnosis, with a 5-year survival rate of approximately 4%.[1]

The first reported genomic alterations demonstrating sensitivity to specific targeted therapies in pulmonary adenocarcinoma were mutations in the epidermal growth factor receptor (EGFR) and rearrangements of the anaplastic lymphoma kinase (ALK). Subsequently, other mutations were identified as new therapeutic targets, including mutations in the B-Raf proto-oncogene (BRAF), and rearrangements of the ROS1 tyrosine kinase proto-oncogene and the neurotrophic tyrosine receptor kinase type 1 (NTRK).[4]

The EGFR is a tyrosine kinase (TK) receptor, whose signaling plays a crucial role in the maintenance and growth of epithelial tissues. The overexpression resulting from mutations in the EGFR gene is associated with the pathogenesis, proliferation, invasion, and metastasis of various solid tumors, including non-small cell lung cancer (NSCLC). This overexpression is observed in approximately 88% of cases of advanced NSCLC.[5]

In Brazil, erlotinib and gefitinib are among the drugs that belong to the therapeutic class of EGFR tyrosine kinase inhibitors, which were incorporated into the treatment list of the Unified Health System (SUS) in 2013, following a favorable recommendation from the National Commission for the Incorporation of Technologies (CONITEC).[6-7] However, molecular testing to identify the mutation and thus make the patient eligible for treatment has not yet been incorporated into the list of available procedures in the SUS, posing a barrier to patient access to these technologies.[8]

Objective

The present study aimed to conduct a budget impact analysis regarding the incorporation of the rt-PCR test for the identification of EGFR mutations, thereby identifying patients eligible for treatment with the drugs erlotinib and gefitinib, which have already been incorporated into the SUS. This is necessary to ensure greater efforts to guarantee access for the Brazilian population to a treatment that is demonstrably more effective.

Methods

For the conduction of this budget impact analysis, the methodological guidelines from the Ministry of Health[9] were utilized, considering the perspective of the Unified Health System (SUS) over a five-year time horizon.

Molecular tests vary from the simplest to the highly complex. Simple tests are designed to detect a specific type of mutation in a particular gene or, in some cases, to identify the most common alterations in one or two genes. Complex tests, especially next-generation sequencing (NGS) tests, can simultaneously detect multiple genetic alterations.[10-11]

The tests vary widely in the information they provide, as well as in sensitivity, specificity, breadth, tissue requirements, and response times. Tests for point mutations, insertions, or deletions are generally based on DNA extracted from tumor tissue. For this purpose, there are numerous methods based on polymerase chain reaction (PCR).[10-11]

This budget impact analysis was developed based on information from the rt-PCR test, due to its low-cost technology compared to complex tests and the fact that there is already installed capacity in Brazil for performing the test.

Target Population
Patients with NSCLC

The data to estimate the eligible population were obtained from the Ambulatory Information System

(SIA/DATASUS), through the files related to the AQ subsystem – APAC for Chemotherapy. These files were processed using the TABWIN application for table extraction. The data extraction was initially performed using the ICD-10 classes, applying them to the "ap_cidpri" field (primary ICD) to filter all records of cases treated by the SUS, positioned in group C34 – Malignant Neoplasm of the Bronchi and Lungs.

Subsequently, a filter was applied with the procedure code registered in the SUS Procedures, Medications, and OPM Management System (SIGTAP) – 0304020214 – CHEMOTHERAPY FOR ADVANCED NON-SMALL CELL LUNG CARCINOMA. This way, the High Complexity Procedure Authorizations (APAC) issued for this clinical indication from 2015 to 2021 were obtained. Following that, filters were conducted to identify potential eligible patients. Initially, only type 1 APACs were selected, excluding continuity ones. The first chemotherapy records for the treatment of lung cancer for each coded National Health Card (CNS) were then selected (variable "AP_CNSPCN"), ordered by the oldest record identified by the treatment start date ("AQ_DTINTR") and the procedure date (variable "AP_CMP"). Duplicate patients were excluded.

Thus, the population treated in the SUS during the period that should have undergone EGFR mutation testing was obtained. To verify if there was linear growth during this period, a regression model was applied, which indicated variable growth. Subsequently, a polynomial regression model was utilized to estimate the eligible population for the rt-PCR test for EGFR mutation identification from 2023 to 2027.

Costs

In this study, only the cost of acquiring the rt-PCR test was applied, as it was assumed that specialized laboratories already exist and have the necessary installed capacity to perform the test, eliminating the need for equipment acquisition or workforce expansion.

For the cost, the realization of one test per patient was considered. The value used was obtained from the public procurement portal, auction No. 37, held in 2023, which corresponds to a purchase made by the National Cancer Institute for the amount of R$ 1,200.00.[12]

Scenarios

For the current scenario, the total number of eligible patients for the test was considered, but who do not undergo it, or who do so using private resources (for example, using vouchers provided by the pharmaceutical industry). Since the procedure code is not currently available in SIGTAP, it was not possible to verify whether any establishment authorized by SUS is already performing the test, how many patients have been tested, and what the existing cost is for the public health system. Thus, it was assumed that, in the current scenario, 100% of patients do not undergo the test through SUS, resulting in zero cost for the system.

For alternative scenario 1, there would be the incorporation of the test with an initial diffusion rate of 20% and a gradual annual increase of 20%. This gradual increase would result from a possible expansion of the healthcare network, making it the more modest scenario.

In a second alternative scenario 2, there would be the incorporation of the test with a more aggressive diffusion rate, starting with 100% of patients undergoing the test from the first year of incorporation, based on the premise that there is already an established demand for the incorporation of treatments. The diffusion rate would remain at 100% over the years, as, despite the existence of other types of tests for the same purpose, the rt-PCR is less costly.

Sensitivity Analysis

The uncertainties attributed to the model parameters were tested in the sensitivity analysis. The parameter chosen to vary in the deterministic analysis was the acquisition price of the rt-PCR, considering that there are different suppliers and brands of the test. A variation of 25% was applied both upwards and downwards, in accordance with the recommendations of the Methodological Guidelines for budget impact analysis from the Ministry of Health.[9]

Results

The population that started chemotherapy as the first line of treatment for advanced or metastatic NSCLC in the Unified Health System was 40,857 individuals. Table 1 presents the number of new users per year.

Table 1. Number of individuals starting chemotherapy as the first line of treatment for non-small cell lung cancer in the Unified Health System, from 2015 to 2021.

Year	Chemotherapy users
2015	5.516
2016	5.558
2017	5.988
2018	5.763
2019	6.041
2020	5.955
2021	6.036

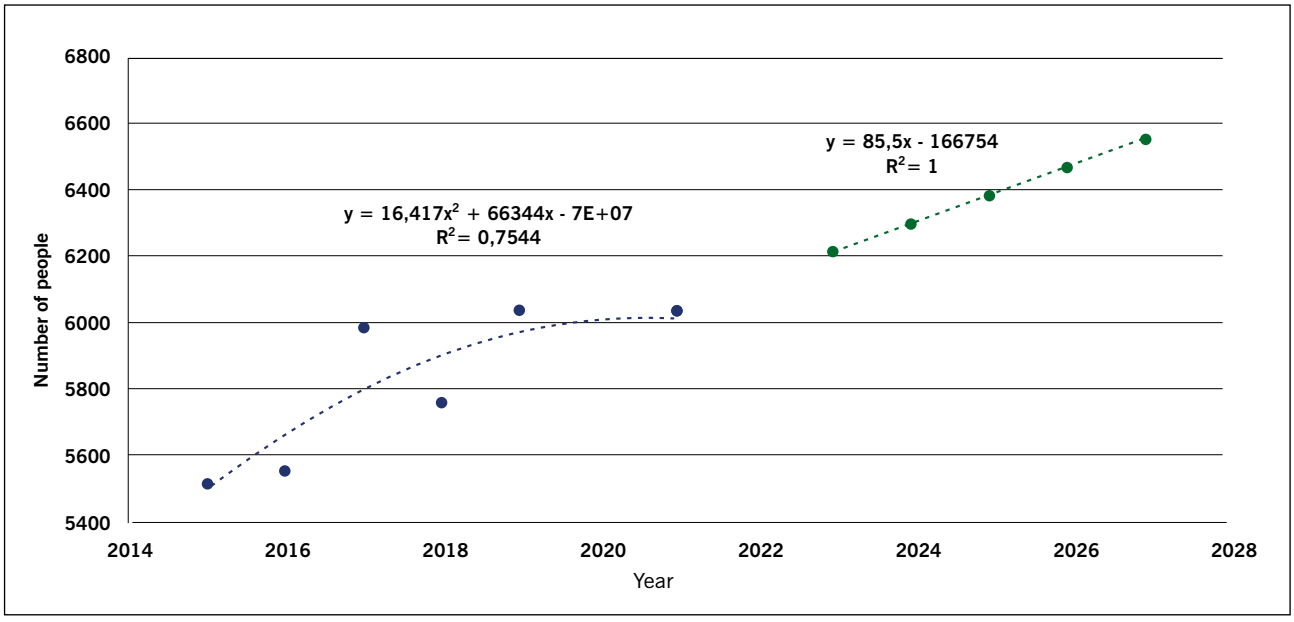
The eligible population to undergo the rt-PCR test from 2023 to 2027 was estimated at 31,918 new individuals. The value of the polynomial correlation coefficient for the historical series (2015-2021) was $R^2 = 0.7544$. After the necessary adjustments, the estimated correlation coefficient for the projected series was $R^2 = 1.0$ (Figure 1).

The budget impact resulting from a possible adoption of the rt-PCR test for the identification of the EGFR gene mutation in patients diagnosed with NSCLC within the SUS, considering a time horizon of 5 years, is presented in Table 2. The estimated total accumulated budget impact over five years for the alternative scenario 1 was R$ 23,186,140.03, and for alternative scenario 2 was R$ 38,301,950.72.

The deterministic sensitivity analysis of alternative 1, showing the best and worst scenarios, is demonstrated in Figure 2. In the best scenario, the budget impact over 5 years was estimated at R$ 17,389,605.03, and in the worst scenario, it was R$ 28,982,675.04.

Figure 3 presents the deterministic sensitivity analysis of alternative 2. In this case, the budget impact over 5 years in the best scenario was estimated at R$ 28,726,463.04, and in the worst scenario at R$ 47,877,438.40.

Figure 1. Demand assessed retrospectively (2015-2021) and estimated eligible population prospectively (2023-2027) for the use of the rt-PCR test for the identification of the epidermal growth factor receptor (EGFR) in patients diagnosed with non-small cell lung cancer within the Unified Health System.



Discussion

The analysis conducted revealed an increase in the population diagnosed with advanced or metastatic NSCLC treated with first-line chemotherapy. The estimated cases for the period of 2023-2027 also showed an upward trend, reinforcing the need for the adoption of molecular diagnostic strategies within the SUS that allow for the selection of the most suitable treatment for patients. The scenario analysis demonstrated that the incorporation of the rt-PCR test could be feasible for the healthcare system, promoting the rational use of the tyrosine kinase inhibitors erlotinib and gefitinib, similar to the incorporation, in 2019, of qualitative and quantitative reverse transcription polymerase chain reaction (RT-PCR and RT-qPCR) tests and in situ hybridization (ISH) for the diagnosis and monitoring of chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL Ph+).[13]

Table 2. Estimation of Budget Impact of adopting the rt-PCR test for the identification of the epidermal growth factor receptor (EGFR) in patients diagnosed with non-small cell lung cancer within the Unified Health System.

Year	Eligible population	Budget Impact (base scenario) (R$)	Alternative Scenario 1		Alternative Scenario 2	
			Diffusion rate	Incremental BI (R$)	Diffusion rate	Incremental BI (R$)
Year 1	6.213	0,00	20%	1.491.143,60	100%	7.455.718,01
Year 2	6.298	0,00	40%	3.023.171,90	100%	7.557.929,74
Year 3	6.383	0,00	60%	4.595.973,29	100%	7.659.955,49
Year 4	6.469	0,00	80%	6.209.984,95	100%	7.762.481,19
Year 5	6.555	0,00	100%	7.865.866,29	100%	7.865.866,29
Total	31.918	0,00	----	23.186.140,03	----	38.301.950,72

Subtitle: BI: Budget Impact

Figure 2. Sensitivity analysis of alternative scenario 1.

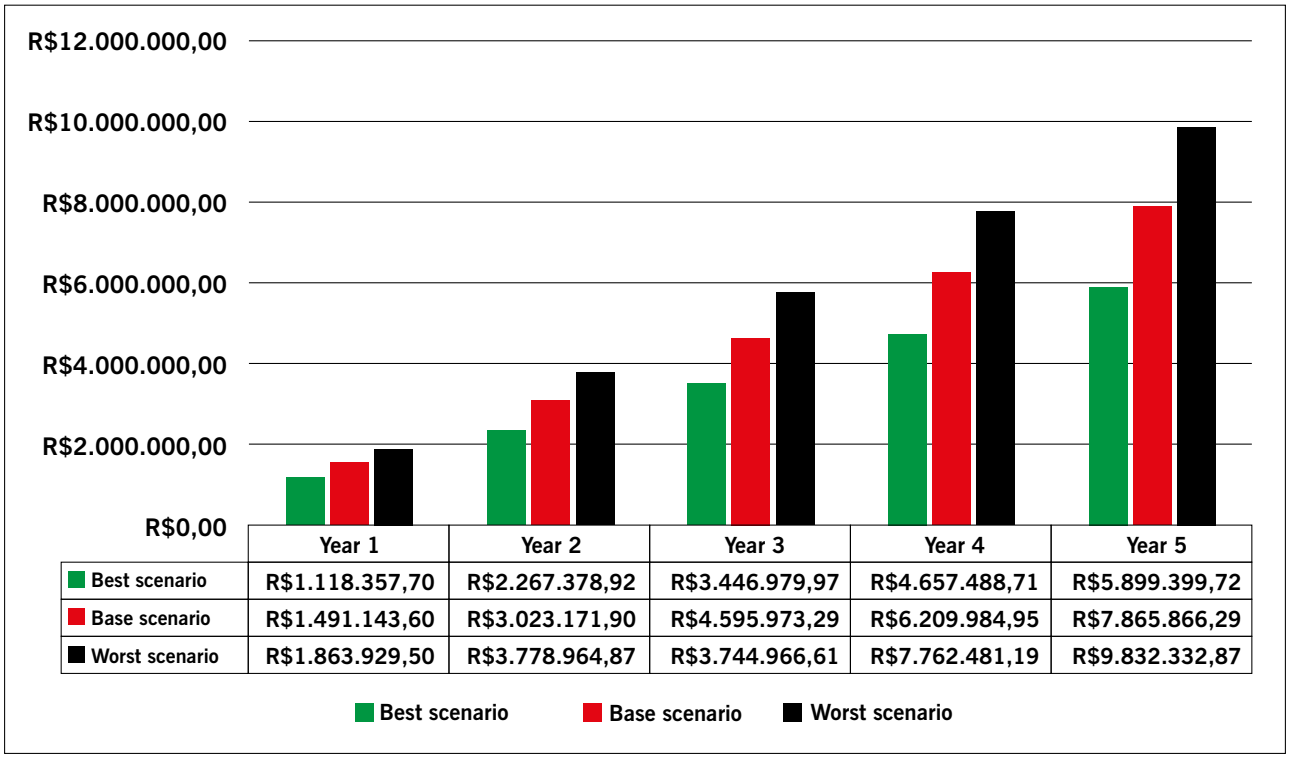
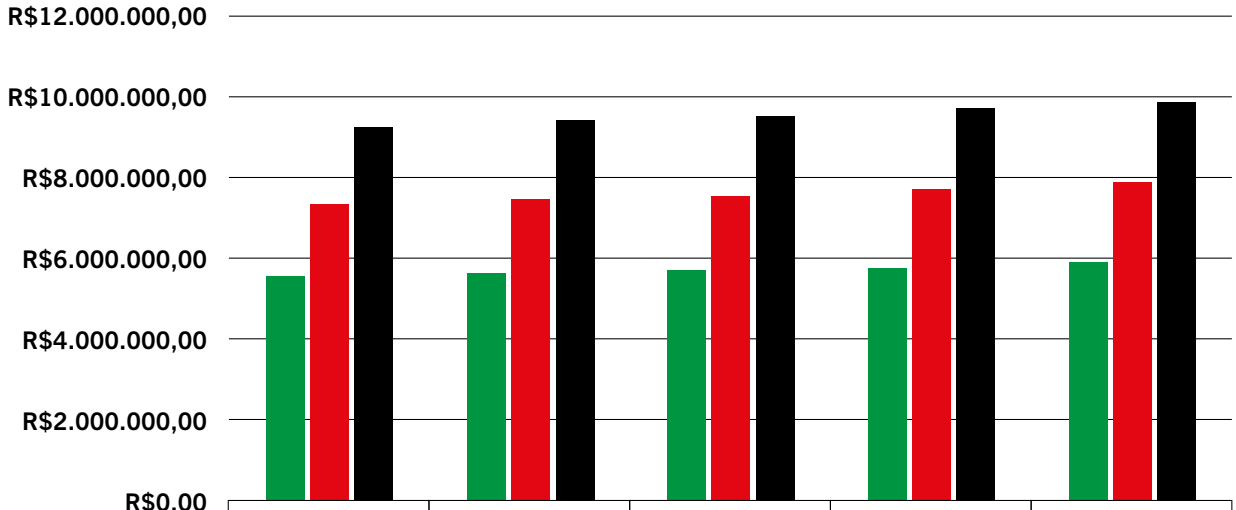


Figure 3. Sensitivity analysis of alternative scenario 2.



	Year 1	Year 2	Year 3	Year 4	Year 5
Best scenario	R$5.591.788,51	R$5.668.447,31	R$5.744.966,61	R$5.821.860,89	R$5.899.399,72
Base scenario	R$7.455.718,01	R$7.557.929,74	R$7.659.955,49	R$7.762.481,19	R$7.865.866,29
Worst scenario	R$9.319.647,52	R$9.447.412,18	R$9.574.944,36	R$9.703.101,49	R$9.832.332,87

The sequencing of the EGFR gene using polymerase chain reaction (PCR) tests is the most widely used method to identify EGFR mutations. This test has been recognized as an important diagnostic tool for patients with NSCLC, helping to identify those eligible for treatment with gefitinib or erlotinib, thereby preventing these tyrosine kinase inhibitors from being prescribed to patients without the mutation and exempting the healthcare system from unnecessary expenses.[14]

The American College of Pathologists, the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) recommend the testing for EGFR and ALK, along with ROS1, HER2, MET, BRAF, KRAS, and RET, in all patients with NSCLC.[10]

However, a global survey by the IASLC on the implementation of these molecular tests in lung cancer revealed that among 102 participating countries across five geographic regions (Asia, Europe, Latin America, United States/Canada), most of the 2,537 participants reported that less than half of patients underwent molecular testing, with EGFR, ALK, and ROS1 being the three most requested molecular tests. The five barriers identified across all regions included the cost of molecular testing, the quality of tissue/testing standards, accessibility, awareness, and turnaround time for tests.[15]

In Brazil, a study utilizing data from a database of 11,684 NSCLC patients treated in public or private services from 2011 to 2016 revealed that only 38% of patients were tested for EGFR mutations (76% in the private sector and 24% in the public service).[15] These data highlighted the scarcity of tests for EGFR mutation identification in the country, the significant disparity between public and private services, and the need to expand access to testing to improve lung cancer survival rates at the national level.

In the same study, researchers conducted EGFR mutation testing on samples received from 3,364 patients between 2011 and 2013, detecting the mutation in 25.5% (n=857) of the samples[16], corroborating findings from another study conducted between 2013 and 2018, where 513 EGFR mutation tests were performed on Brazilian patients, and the mutation was detected in 22.5% of those patients.[4]

Based on this mutation frequency in the Brazilian population, an analysis of the usage data for the medications erlotinib and gefitinib after their incor-

poration into the SUS from 2014 to 2021 revealed that the number of patients receiving the medication was about 50% below what would be expected, considering that a total of 342,271 individuals diagnosed with advanced or metastatic NSCLC were treated with first-line chemotherapy during this period.[17] One reason for this low utilization of the medications may be the lack of testing. Thus, it can be inferred that the incorporation of the rt-PCR test could significantly impact the increased use of these medications.

Although the rt-PCR test currently represents an unmet need, it is crucial to pay attention to other molecular alterations that occur in tumors, as previously recommended by pathology experts. Therefore, the possibility of incorporating other tests or multi-gene tests should be considered to guide therapeutic choices.

It is important to highlight that the *market share*, which corresponds to the rate of diffusion and incorporation of technology in the market, in budget impact analyses based on real-world data, must consider the level of knowledge that healthcare professionals already have about the new technology and the potential for extending its current use as determinants of the speed of incorporation.[18] Based on these assumptions, the current analysis started from the premise that healthcare professionals have a high awareness of the importance of using the rt-PCR test for the identification of EGFR mutations and that there is already installed capacity to allow for rapid expansion of the technology's use in Brazil.

The budget impact values presented in this analysis should be considered with caution, as the calculations were based on the cost of a single type and brand of test, and the population was estimated using regression.

Conclusion

The total budget impact estimate for the period, considering a more modest scenario with a diffusion rate of 20% per year, was approximately R$ 23 million over 5 years. In a more aggressive scenario, with 100% diffusion, the estimated incremental impact was approximately R$ 38 million.

Contributions of the authors
MJSS: conception and planning of the study, as well as data analysis and interpretation; IPP: investigation and interpretation of the data; WF: planning of the study and data analysis and interpretation; AL: conception and planning of the study, as well as data analysis and interpretation; All authors contributed to the writing and/or critical revision and final approval of the manuscript version.

Conflicts of Interest
The authors have no conflicts of interest related to this work.

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