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ORIGINAL RESEARCH

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Cost-effectiveness analysis of molecular diagnosis by next-generation sequencing versus sequential single testing in metastatic non-small cell lung cancer patients from a south Spanish hospital perspective

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ABSTRACT

Background: To assess the cost-effectiveness of using next-generation sequencing (NGS) compared to sequential single-testing (SST) for molecular diagnostic and treatment of patients with advanced non-small cell lung cancer (NSCLC) from a Spanish single-center perspective, the Hospital Universitario Virgen del Rocio (HUVR).

Research design and methods: A decision-tree model was developed to assess the alterations detection alterations and diagnostic cost in patients with advanced NSCLC, comparing NGS versus SST. Model inputs such as testing, positivity rates, or treatment allocation were obtained from the literature and the clinical practice of HUVR experts through consultation. Several sensitivity analyses were performed to test the robustness of the model.

Results: Using NGS for molecular diagnosis of a 100-patients hypothetical cohort, 30 more alterations could be detected and 3 more patients could be enrolled in clinical-trials than using SST. On the other hand, diagnostic costs were increased up to €20,072 using NGS instead of SST. Using NGS time-to-results would be reduced from 16.7 to 9 days.

Conclusions: The implementation of NGS at HUVR for the diagnostic of patients with advanced NSCLC provides significant clinical benefits compared to SST in terms of alterations detected, treatment with targeted-therapies and clinical-trial enrollment, and could be considered a cost-effective strategy.

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Non-small cell lung cancer (NSCLC); molecular profiling; oncogenic drivers; cost-effectiveness; next-generation sequencing; sequential single testing

1. Introduction

Lung cancer is the fourth most common type of cancer in Europe, and the leading cause of cancer death worldwide [1]. The Spanish Society of Medical Oncology (SEOM) estimates that, in Spain, lung cancer will be one of the most frequently diagnosed cancers with 29,549 cases in 2021, especially affecting males, which will account for 21,578 cases as compared to 7,971 cases in females [2]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases [3]. About 70% of the patients with NSCLC are diagnosed with advanced disease at the time of diagnosis, most of them being unsuitable for curative treatment [4].

NSCLC has become a leading example of precision medicine success in the treatment of solid tumor malignancies [5]. Clinical management of NSCLC currently relies on surgical, chemotherapeutic, and radiation treatment regimens based on pathology findings and clinical staging, as well as targeted therapies based on molecular profiling [5]. The identification of epidermal growth factor receptor (EGFR) activating mutations and its association with response to drugs such as gefitinib has led to the discovery of several molecular subtypes and oncogenic markers that allow the use of targeted therapies in NSCLC treatment. These include translocations in the anaplastic lymphoma kinase gene (ALK) or the proto-oncogene tyrosine-protein kinase 1 (ROS1) [6]; RET proto-oncogene rearrangements; BRAF proto-oncogene and human epidermal growth factor receptor 2 (HER2) mutations; mesenchymal-epithelial transition factor (MET) mutations; neurotrophic tyrosine kinase (NTRK) gene rearrangements; and Kirsten rat sarcoma viral oncogene (KRAS) mutations [7,8].

Identifying patients with specific genomic alterations is considered as a crucial action to individualize the treatment and improve the outcomes in patients with NSCLC, as targeted therapies have shown a significant improve in progression-free survival (PFS) and treatment response [9]. With that known, and as different treatments are available nowadays and may be used in combination or sequentially to surpass resistance mechanisms, the main goal in the clinical management of patients with NSCLC is to individualize the course of treatments for the patients with the most effective options [10].

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Currently, Next-Generation Sequencing (NGS) is included in the latest updates of the National Consensus guidelines of the Spanish Society of Pathology (SEAP) and SEOM among the techniques that allow the detection of oncogenic molecular markers [11]. NGS is a technology that allows the evaluation and characterization of the nucleic acid sequences of hundreds or thousands of genes at the same time at a relatively low cost. This technique is widely used in oncology, particularly in metastatic cancer diagnosis, to determine mutations in tumor tissue samples [12]. However, in recent years, NGS is only applied to the diagnosis of a small percentage of NSCLC patients, as a few practical barriers hinder its wider adoption, among these, limited patient access, lack of awareness and dissemination within health-care teams about the benefits of NGS, or limited healthcare coverage [9]. In addition, given the relatively recent development of NGS, there is an unmet need to better understand the economic implications of using NGS as compared to other testing strategies in real-world clinical practice [9].

The aim of this study is, by means of a theoretical model, to analyze the cost-effectiveness of using the NGS panel for the detection of genetic molecular subtypes and oncogenic markers in patients with advanced NSCLC at a south-Spain referral hospital, compared to the sequential single-testing (SST) of the same oncogenic markers included in the NGS panel.

2. Methods

The present analysis is a pilot-study based on the routine clinical practice of professionals at the Hospital Universitario Virgen del Rocío (HUVR) in Seville (Spain), specifically the experts consulted were two pathologists and one medical oncologist. Therefore, it is not based on real-word data gathered at the hospital, but on consultations with the experts of the hospital.

2.1. Model structure

A decision-tree model was developed (MS Excel 2010) to assess the detection of alterations and the associated diagnostic cost in patients with NSCLC, comparing the utilization of NGS versus SST. In addition to the decision-tree, which allows us to determine the alterations detected and the costs of the diagnostic phase, a long-term exploratory analysis has been carried out by means of partitioned survival models (PSM) with three health states: progression-free, progressed-disease, and death. Depending on the molecular profile obtained in the decision-tree, the treatment is allocated, and the costs and long-term health consequences are estimated using the PSM (one for each treatment) (Figure 1).

The hypothetical cohort of patients was defined as patients newly diagnosed with advanced or metastatic non-squamous NSCLC or squamous NSCLC who were never smokers, with an unknown genomic alteration status. Therefore, the hypothetical cohort of patients entered the decision-tree model and molecular diagnosis is performed either with NGS or SST (PD-L1 expression is always determined separately in both comparison alternatives), and depending on the test result an appropriate first-line treatment is allocated and patients enter the corresponding PSM. As alterations analyzed are mutually exclusive, in SST the sequence is stopped in case of a positive result and the corresponding first-line treatment is initiated.

The time horizon used in the decision-tree comprises only the diagnostic phase of NSCLC patients, while the time horizon considered in the exploratory long-term analysis is

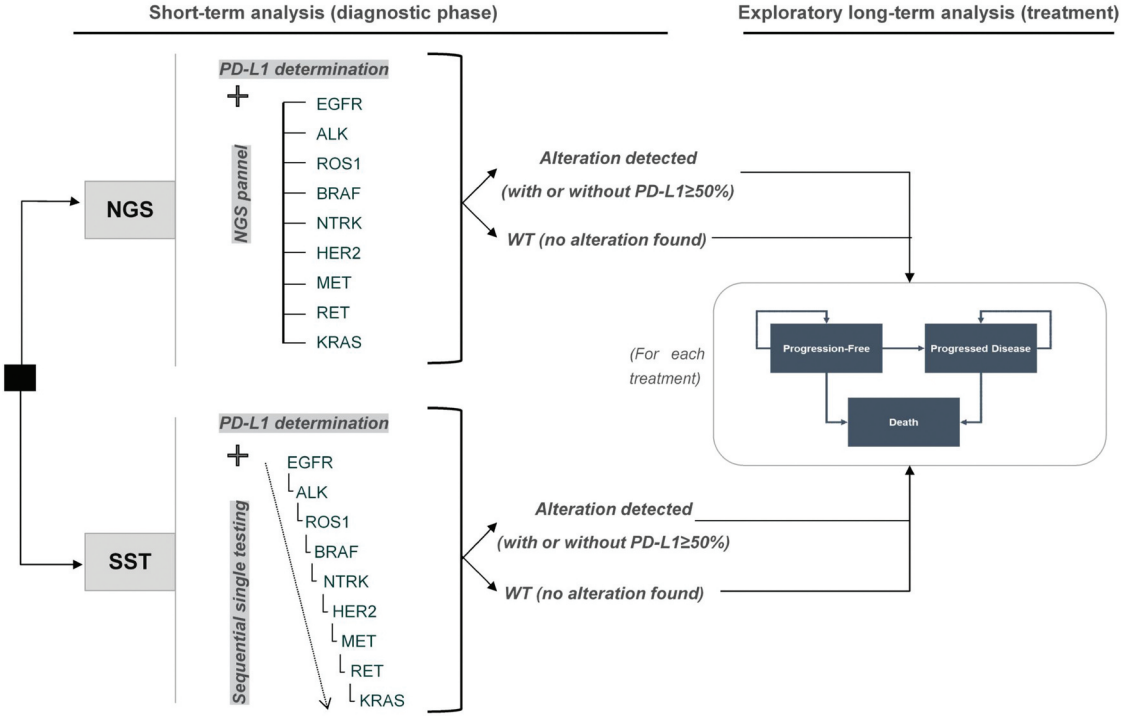

Figure 1. Diagram of the model.

lifetime. The PSM models use monthly cycles, and a 3% discount rate for both costs and health outcomes was applied in the exploratory long-term analysis.

Health outcomes of the diagnostic phase were expressed as additional patients eligible for target therapy (peTT) and the additional patients who may be enrolled in clinical trials (peCT). Costs were expressed in euros (€) of 2022 and only direct medical costs were considered. Incremental cost-effectiveness ratios (ICERs) were calculated for both peTT and peCT. In addition, the model also allows to estimate the time required to obtain the diagnostic results (time-to-results) with each of the two methodologies compared (NGS and SST). In the long-term exploratory analysis, health outcomes were expressed as life years (LY), and quality-adjusted life years (QALYs), also Incremental cost–utility ratio ICURs were calculated.

In the decision-tree model, the probability of requiring a re-biopsy due to tissue exhaustion was included. In this case of insufficient tissue, the model assumed the need for a re-biopsy, which could be successful or not. The estimate of tissue exhaustion and the successive probability of re-biopsy was obtained from the economic evaluation performed by Pennell et al. [9]. Therefore, in line with this article, 8% of the patients were assumed to require a re-biopsy to continue testing due to tissue exhaustion. Of these patients, only 30% were assumed to be actually re-biopsied, with 15% of those patients experiencing failure with re-biopsy [9].

2.2. Clinical practice in the Spanish single center

In the following section, all clinical inputs that have been obtained from the literature or expert interviews are described.

For ease of reading, absolute results are shown for a hypothetical cohort of 100 patients. In any case, this figure is close to the patients with advanced or metastatic non-squamous NSCLC or squamous NSCLC who were never smokers that are treated yearly in the HUVR, according to the experts.

In the model, the testing rate was defined as the percentage, according to clinical practice, in which the determination of the biomarker is finally performed over the hypothetical total of patients. It was assumed that for NGS the testing rate is always 100% for all biomarkers (all present mutations are detected). The testing rates for the SST in the HUVR were defined by the experts (Table 1).

Also, the positivity rate was defined as the mutation/rearrangement rate detected in the biomarkers considered in the analysis. The positivity rate in the hypothetical cohort of patients was assumed to be the same regardless of the diagnostic method. Positivity rates of EGFR, ALK and ROS1 were obtained from LungPath database [13] and from the European Thoracic Oncology Platform Lungscape Project for KRAS G12C [14]. All figures were validated by the experts, who provided the positivity rates for the rest of biomarkers based on their usual practice at the HUVR (Table 1).

To determine the time-to-results with both NGS and SST, the HUVR experts established the time required for each of the tasks that comprise the diagnostic phase (pre-analytical and analytical subphases), as well as the working days required for each technique in the analytical phase (Table 2).

Table 1. Testing and positivity rates.

	Testing rate		
Biomarker	NGS	SST	Positivity rate
EGFR	100.00%	100.00%	13.60%
ALK	100.00%	100.00%	3.40%
ROS1	100.00%	100.00%	2.00%
BRAF $_{V600}$	100.00%	60.00%	5.50%
NTRK	100.00%	20.00%	1.00%
HER2	100.00%	0.00%	3.80%
MET	100.00%	20.00%	4.40%
RET	100.00%	20.00%	2.10%
KRAS G12C	100.00%	20.00%	17,00%
PD-L1	100.00%	100.00%	33.00%

EGFR, epidermal growth factor receptor gene; ALK, anaplastic lymphoma receptor kinase gene; ROS1, ROS proto-oncogene 1, receptor tyrosine kinase; BRAF, B-Raf proto-oncogene, serine/threonine kinase; NTRK, neurotrophic tyrosine receptor kinase gene; HER2, human epidermal growth factor receptor 2 gene; MET, MET proto-oncogene; RET, RET proto-oncogene; KRAS, KRAS proto-oncogene; PD-L1, programmed death-ligand 1; RT-PCR, reverse transcription polymerase chain reaction; IHQ, immunohistochemistry; FISH, fluorescence in situ hybridization.

These times were included in the decision tree in order to calculate the average time to complete diagnostic results.

As shown in Figure 1, after the diagnostic phase, treatments are allocated according to the alterations detected by the decision tree. Given that PD-L1 expression is determined by IHQ in parallel to the NGS panel and non-CCP sequence, and since PD-L1 overexpression can be found simultaneously with a mutation/rearrangement in a biomarker, treatment allocation is established based on

- Whether or not alteration (mutation/rearrangement) in a biomarker has been detected.
- In addition to this alteration, there is overexpression of PD-L1 or not (TPS ≥50% or TPS <50%).

The table with treatment allocation defined by HUVR experts is shown in supplementary material (table S1). Most of target

Table 2. Time spent and duration of pre-analytical and analytical phases.

	Technician time	Physician time	Shedule (day)
Pre-analytical subphase			
Reception/labelling	5 min	-	Day 0
Fixation	12–16 h	-	Day 0
Macroscopic study	5–10 min	-	Day 0
Processing	12 h (overnight)	-	Day 0
Embedding	15–20 min	-	Day 1
Section cutting	20 min	-	Day 1
Staining	1.5 h	-	Day 2
Pathological diagnostic	-	20 min	Day 2
Analytical subphase			
RT-PCR	2 h per sample	0.5 h per sample	Day 2+ (1–2 working days)
IHQ	2 h per sample	0.1 h per sample	Day 2+ (1 working day)
FISH	2 h per sample	0.5 h per sample	Day 2+ (2 working days)
NGS	30 min per sample	2 h per sample	Day 2+ (7 working days)

RT-PCR, real-time polymerase chain reaction; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; NGS, next-generation sequencing.

therapies included in the model are currently available in HUVR (osimertinib and afatinib for EGFR+; alectinib for ALK+; crizotinib for ROS1+; combination of dabrafenib+trametinib for $BRAF_{V600}$+; larotrectinib for NTRK+) reimbursed by the Spanish National Health Service (NHS) or under compassionate-use programs or foreign medication (i.e. larotrectinib). Other alterations do not currently have approved targeted therapies (0% in the table S1) so enrollment in clinical trial is the only way to access targeted therapies (capmatinib for MET +; praseltinib for RET+; sotorasib for KRAS G12C+).

In the PSM frequently used in oncology, the transition between health states based on the efficacy of treatments is associated with the evolution of PFS and overall survival (OS) curves. Because the follow-up period of clinical trials is shorter than the time horizon considered in pharmacoeconomic models (usually the patient's lifetime), it is necessary to fit parametric curves to the data reported in clinical trials, to extrapolate PFS and OS data beyond the follow-up period. Therefore, for the exploratory long-term analysis, it was needed to extrapolate PFS and OS up to a lifetime horizon. Since the model includes multiple treatments for which individualized data are not available, exponential models were used for all treatments, despite that some treatments might show a better fit to other parametric models.

The median PFS, OS and estimated parameters for the exponential model for each treatment are shown in supplementary material (table S2). Some of the median PFS and OS figures shown in table S2 have only been used to model efficacy in the clinical trial group, since these targeted therapies have not yet been approved (0% allocation in table S1).

Also, for the exploratory long-term analysis, it was required to assign utility values and management costs to each PSM health state.

The utilities assigned to PSM health states, were those reported by Chouaid et al. [15]. Therefore, utility values of 0.71 for progression-free health state and 0.67 for patients with progressive disease were included in our model [15].

Regarding the usual management of patients with advanced NSCLC (both with progression-free disease or progressed disease), in the absence of real-world data from the HUVR, the experts established a standard and common use of resources for all patients according to their clinical experience as follows: one monthly visit to the oncologist along with one complete blood count, one monthly visit to primary care, and one CT scan every 3 months.

2.3. Cost inputs

The analysis was carried out from the perspective of the Spanish National Health System; therefore, the following direct medical costs were included:

- Diagnostic costs (short-term analysis): cost of acquisition of SST or NGS panel; staff costs; costs of possible re-biopsies due to tissue exhaustion.
- Treatment related costs (exploratory long-term analysis): drug acquisition and administration costs; disease management costs.

Table 3. Unit cost for NGS and SST.

Biomarker tested	Technique used	Unit cost (€)
NGS		
All biomarkers	Oncomine Focus Assay	600.00
SST[a]		
EGFR	RT-PCR	105.00
ALK	IHC and FISH	48.40
ROS1	IHC and FISH	62.92[b]
$BRAF_{V600}$	RT-PCR	105.00
NTRK	IHC	96.80[c]
MET	FISH	185.50[d]
RET	FISH	121.00
KRAS G12C	RT-PCR	105.00
PD-L1	IHC	30.25

EGFR, epidermal growth factor receptor gene; ALK, anaplastic lymphoma receptor kinase gene; ROS1, ROS proto-oncogene 1, receptor tyrosine kinase; BRAF, B-Raf proto-oncogene, serine/threonine kinase; NTRK, neurotrophic tyrosine receptor kinase gene; MET, MET proto-oncogene; RET, RET proto-oncogene; KRAS, KRAS proto-oncogene; PD-L1, programmed death-ligand 1; RT-PCR, reverse transcription polymerase chain reaction; IHQ, immunohistochemistry; FISH, jluorescence in situ hybridization.

[a]HER2 is not shown as its testing rate is 0%, as shown in Figure 1.

[b]Weighted average of 80% IHC and 20% FISH.

[c]Weighted average of 80% IHC and 20% FISH (three determinations for three genes, NTRK 1-2-3).

[d]Weighted average of 50% FISH (amplifications) and 50% RT-PCR (MET ex14 skipping).

Table 3 shows the unit cost for SST and the NGS panel [16] in the HUVR determined by the experts.

Regarding the staff cost, to establish the cost per hour for technicians and physicians, the gross annual salary was obtained from the Andalusian Health Service (group A1 level N.28 for physician, group C1 level N.17 for technician) [17]. Cost per hour was calculated by dividing gross salary by 52 weeks and 40 hours, adding the percentage of Social Security contribution paid by the Spanish State for health personnel, 31.05% in 2019 [18], obtaining a cost of €15.94 per hour for specialist technicians and €45.65 - per hour for physicians.

If a re-biopsy is performed due to tissue exhaustion, a unit cost of €555.70 was assigned for a solid biopsy procedure [19].

Finally, for the treatment-related costs used in the exploratory long-term analysis, all drug costs are expressed as the ex-factory price considering the corresponding deductions according to RDL 08/2010 [20] when applicable. It was assumed that patients enrolled in clinical trials do not entail a cost for the hospital.

For drugs where the dose is not fixed, a mean body surface area of 1.80 m^2 and a mean weight of 70 kg (assumption), and vial sharing was assumed.

Summary of drug acquisition cost and administration cost are shown in supplementary material (table S3).

Health-care resource unit costs used to estimate the disease management costs were obtained from the Spanish health-care database eSalud: oncologist visit, €88.38; primary care visit, €37.42; complete blood count, €67.22; TC scan, €44.52 [19].

2.4. Sensitivity analysis

Sensitivity analyses have been performed, both deterministic and probabilistic, with the main goal of evaluating the uncertainty related to some of the parameters that were included in

the model, as well as to verify the robustness of the results obtained in the carried-out analysis.

One-way sensitivity analysis was used to assess the influence of some key parameters on the model results (ICER expressed as € per peTT and € per peCT) by modifying the parameters individually by ±20% with respect to the base case value.

In the probabilistic sensitivity analysis (PSA), 1,000 simulations were run by second-order Monte Carlo methodology, simultaneously modifying selected variables with an established distribution [21]. The prevalence of mutations/rearrangements in selected biomarkers and the probability of rebiopsy in case of an invalid result were modified by a normal distribution, and unit costs were modified following a gamma distribution.

3. Results

In the 100-patients hypothetical cohort, with routine use of the NGS panel for molecular diagnosis of patients in the HUVR, 30 more alterations could be detected than by performing individualized determination by SST, as shown in Figure 2.

Thanks to this higher rate of detection of alterations with the use of NGS, it would be possible to increase the number of patients enrolled in clinical trials of new targeted therapies. Specifically, in the HUVR it is estimated that three more patients could be recruited compared with SST, which represents an increase of 38.1%.

Table 4 shows the results of the efficacy variables defined peTT and peCT, as well as the total diagnostic costs. The calculated cost-effectiveness ratios show that, despite the slight increase in diagnostic costs (€18,590), using NGS in the HUVR is a cost-effective strategy compared to SST, when we consider peTT and peCT as efficacy variables (€617 per peTT gained and €6,249 per peCT gained). The benefit of using NGS not only translates into a greater number of alterations detected and therefore more patients treated with targeted therapies or included in clinical trials, it also allows to have a complete molecular profile earlier, and therefore start treatment earlier having all the information.

The time-to-results analysis reveals that NGS panel results would be available in 9 days on average, whereas with the SST, the determination of all biomarkers would not be completed until day 16.7 on average (Figure 3).

Regarding the exploratory long-term analysis shown in Table 5, the inclusion of treatment costs means that the overall costs (diagnostic + treatment) with NGS are higher than with SST (€47,432 incremental euros associated to NGS strategy), as more patients are treated with targeted therapies and these usually have a higher cost. On the other hand, the increased use of targeted therapies associated with NGS also provides better health outcomes (expressed in LY and QALYs) compared to diagnosis by SST (7.9 LY gained and 5.22 QALYs gained). Exploratory ICURs show that, analyzing the long-term costs and benefits of NSCLC treatments, molecular diagnosis by NGS remains a cost-effective strategy versus SST.

3.1. Sensitivity analysis

Results of the one-way sensitivity analysis, represented by two tornado diagrams for both peTT and peTC as efficacy variables, are shown in Figure 4.

Variables affecting more the ICER, both for peTT and peTC as efficacy variables, are testing costs (NGS panel and individual tests). In any case, the results of the base case are robust.

Lastly, Figure 5 shows the PSA results represented in a cost-effectiveness scatter plot, in which the ordinate axis represents the costs and the abscissa axis the number of patients (including the peTT and peCT variables).

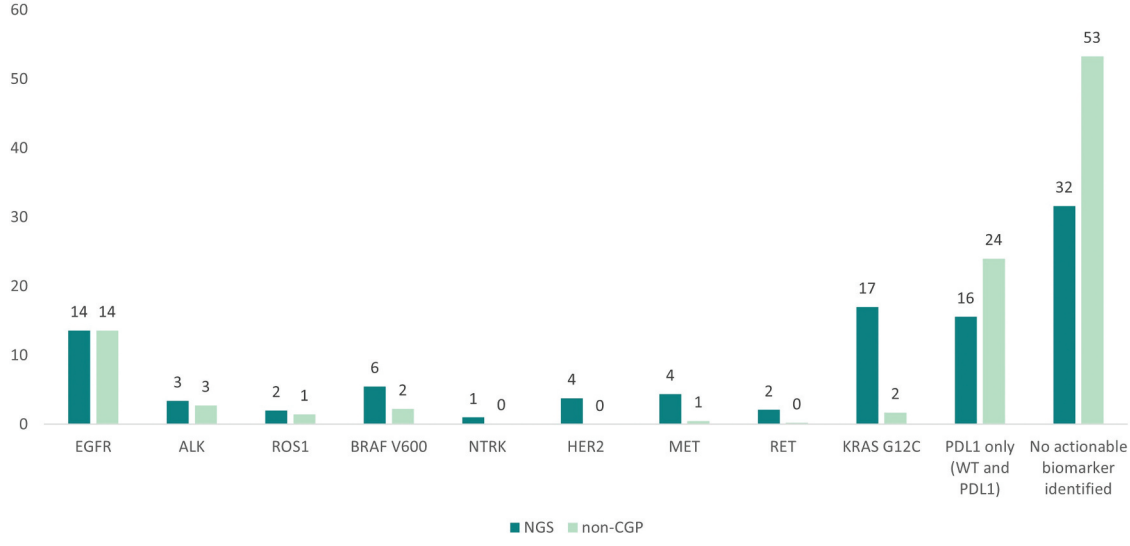

Figure 2. Distribution of alterations detected in hypothetical cohort.

EGFR, epidermal growth factor receptor gene; ALK, anaplastic lymphoma receptor kinase gene; ROS1, ROS proto-oncogene 1, receptor tyrosine kinase; BRAF, B-Raf proto-oncogene, serine/threonine kinase; NTRK, Neurotrophic tyrosine receptor kinase gene; HER2, human epidermal growth factor receptor 2 gene; MET, MET proto-oncogene; RET, RET proto-oncogene; KRAS, KRAS proto-oncogene; PD-L1, programmed death-ligand 1.

Table 4. Short-term cost and efficacy outcomes.

	NGS	SST	Incremental
Total diagnostic costs (€)	122,012	103,422	+18,590
Testing cost (€)	*63,025*	*32,112*	*+30,913*
Re-biopsy cost (€)	*0*	*6,351*	*−6,351*
Staff cost (€)	*58,987*	*64,960*	*−5,972*
peTT	53	23	+30
peCT	11	8	+3
ICER (expressed as additional € per peTT gained)			**€617/peTT**
ICER (expressed as additional € per peCT gained)			**€6,249/peCT**

NGS, next-generation sequencing; SST, sequential single testing; peTT, additional patients eligible for target therapy; peCT, additional patients eligible for enrollment in clinical trials; ICER, incremental cost–effectiveness ratio.

4. Discussion

The ability to identify molecular alterations in advanced NSCLC has evolved rapidly [22]. Together with the growing number of targeted therapies available that have significant activity in oncogenic cancers, biomarker testing has transformed the therapeutic landscape for patients with this disease, promoting therapeutic interventions that positively impact the lives of these patients [22].

By detecting a greater number of tumor molecular alterations, the use of NGS-based testing is associated with an increased use of targeted therapies and therefore an increased patient overall survival [23–25]. In turn, targeted therapies reduce the use of health-care resources, namely hospitalizations and emergency department visits, versus patients who did not receive these treatments [26]. Therefore, using NGS to identify patients who could benefit from targeted treatments not only improves their overall survival but may also result in healthcare resource savings. Additionally, it has been reported that the introduction of NGS could save between €25 and €1,041 compared to standard diagnostic techniques if a minimum number of patients were tested and that this expenditure reduction increases with the number of mutations analyzed [27–29]. In addition, molecular diagnosis with NGS techniques has shown similar or even shorter diagnosis generation times than sequential testing techniques [9,29]. However, despite the benefits associated with NGS, cost-effectiveness analyses on the implementation of these techniques for the diagnosis of NSCLC patients have been carried out in a few countries [8,25,30,31], whereas there is no available published evidence for Spain.

Pathology departments should work in coordination with the other services involved in the diagnosis and treatment of patients with NSCLC to optimize the available resources and the clinical management of these patients [32]. Therefore, to evaluate the efficacy in the management of advanced NSCLC patients in Spain, a comprehensive approach to molecular diagnosis together with pharmacological treatment is essential [32]. Our pilot-study is the first one to date that evaluates the cost-effectiveness of the NGS-based NSCLC testing in comparison with the individualized determination of biomarkers in Spain. A more comprehensive analysis, carried out in a national context, will be carried out to complement this pilot-study.

The pilot-analysis carried out in a single-center context showed that the NGS strategy is clearly cost-effective compared to SST when peTT and peCT are considered as efficacy parameters, taking into account that the cost-effectiveness thresholds usually considered in our country use LY or QALY as efficacy variables [33,34]. The higher acquisition cost of the NGS panel is partially offset by savings in the re-biopsy and staff costs. In addition, a greater number of patients included in clinical trials also help to reduce hospital treatment costs. In the exploratory long-term analysis, NGS remains a cost-effective strategy versus SST when the treatment cost is considered and LY and QALY are the efficacy variables. The growing need to study emerging biomarkers (HER2, MET, RET, NTRK, etc.) in addition to the biomarkers considered mandatory in the current Spanish guidelines, warrants the establishment of a routine and more comprehensive molecular assessment with NGS [11]. Our results reinforce the cost-effectiveness of NGS compared to SST in different scenarios, supporting the recommendations of the national guidelines. In any case, although our exploratory long-term results should be taken with caution as they represent a single-center, it seems that the RCEI obtained are below the thresholds of €22,000–30,000/LY or QALY usually considered in Spain [33,34].

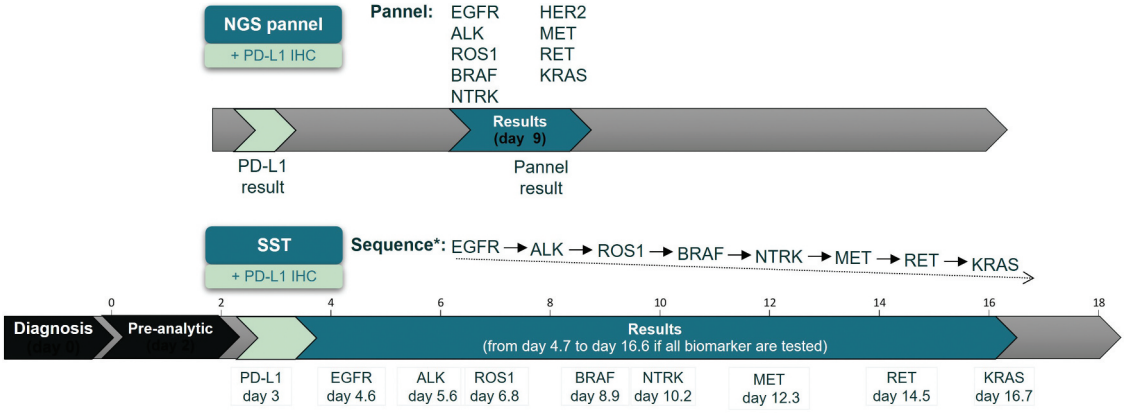

Figure 3. Time-to-results analysis.

NGS, next-generation sequencing; SST, sequential single testing; EGFR, epidermal growth factor receptor gene; ALK, anaplastic lymphoma receptor kinase gene; ROS1, ROS proto-oncogene 1, receptor tyrosine kinase; BRAF, B-Raf proto-oncogene, serine/threonine kinase; NTRK, neurotrophic tyrosine receptor kinase gene; MET, MET proto-oncogene; RET, RET proto-oncogene; KRAS, KRAS proto-oncogene; PD-L1, programmed death-ligand 1* HER2 is not shown as its testing rate is 0%, as shown in Table 1.

Table 5. Exploratory long-term results.

	NGS	SST	Incremental
Diagnostic costs (€)	122,012	103,422	+18,590
Treatment costs (€)	11,368,232	11,339,390	+28,843
Total overall costs (€)	**11,490,245**	**11,442,812**	**+47,432**
LYs	276.77	268.87	+7.90
QALYs	185.96	180.74	+5.22
ICER (expressed as additional € per LY gained)			**€6,005/LY**
ICUR (expressed as additional € per QALY gained)			**€9,084/QALY**

NGS, next-generation sequencing; SST, sequential single testing; LY, life years; QALY, quality-adjusted life years; ICER, iIncremental cost-effectiveness ratio; ICUR, incremental cost–utility ratio.

The comprehensive approach described has previously been used in some economic evaluations. Specifically in the US, the cost-effectiveness of using a NGS panel with more than 30 genes versus SST in the diagnosis of patients with advanced stage NSCLC was analyzed from the payer's perspective, obtaining a ICER of $148,478/LY for NGS >30 genes versus SST [25]. In Brazil, the cost-effectiveness of an NGS panel compared to individual EGFR determination in patients with metastatic, non-squamous NSCLC was analyzed from the perspective of the Brazilian Private Health System, reporting that NGS is a dominant alternative reducing cost compared to individual EGFR determination and improving PFS [30]. Also in Brazil, a recent study evaluated the cost-effectiveness of NGS versus other RT-PCR and FISH to identify the EGFR status and the translocation of ALK and ROS1 [31]. In this case, NGS testing was not cost-effective in terms of QALYs in patients with advanced NSCLC adenocarcinoma histology [31]. Another cost-effectiveness analysis carried out in an Asian NSCLC population compared the performance of NGS panels with traditional assays. In line with our findings, NGS testing implementation would allow the identification of additional patients that could receive appropriate personalized therapy [8]. Outside the scope of cost-effectiveness analyses, the study conducted by Pennell et al. [9] in 2019 in the USA aimed to evaluate the economic impact associated with the use of the NGS panel versus the use of isolated biomarker testing in patients with metastatic NSCLC. In line with our findings, their results showed lower cost and shorter time to results from NGS with respect to other diagnostic techniques [9]. Scenario specificities may account for the differential outcomes of cost-effectiveness analyses, these include the NGS panel size and the comparator considered, the country-specific cost of the intervention, the time-specific health outcomes analyzed, and the efficacy variables included in the analysis.

Our analysis is not exempt of some limitations. Some are inherent to pharmacoeconomic models, that stem from their structural rigidity hindering a complete representation of usual clinical practice. Also, our pilot-analysis is performed from the perspective of a single center, conducting interviews with professionals of that center. It should also be noted that other centers with resource constrained may not have the capacity to undertake the implementation of NGS, given that an initial investment and trained personnel are required. Therefore, the transferability of the results to other settings is limited, and a further analysis from a broader perspective is needed.

Regarding the identification of alterations using NGS or SST by means of the decision-tree model, real-world data were not available, so certain assumptions had to be made. The prevalence of mutations/rearrangements was assumed to be the same regardless of the diagnostic method used (NGS or SST). That means that the higher testing rate with NGS (100% assumption) is what causes a higher number of mutations to be detected. Also, the NGS panel used can provide different results, in the case of our pilot a panel of 52 genes was studied. It is therefore likely that our results are underestimated, since there are rare mutations, such as *BRAF* K601E and *EGFR* exon 20 insertion, which cannot be detected by SST and can be detected by NGS [35]. Also, it

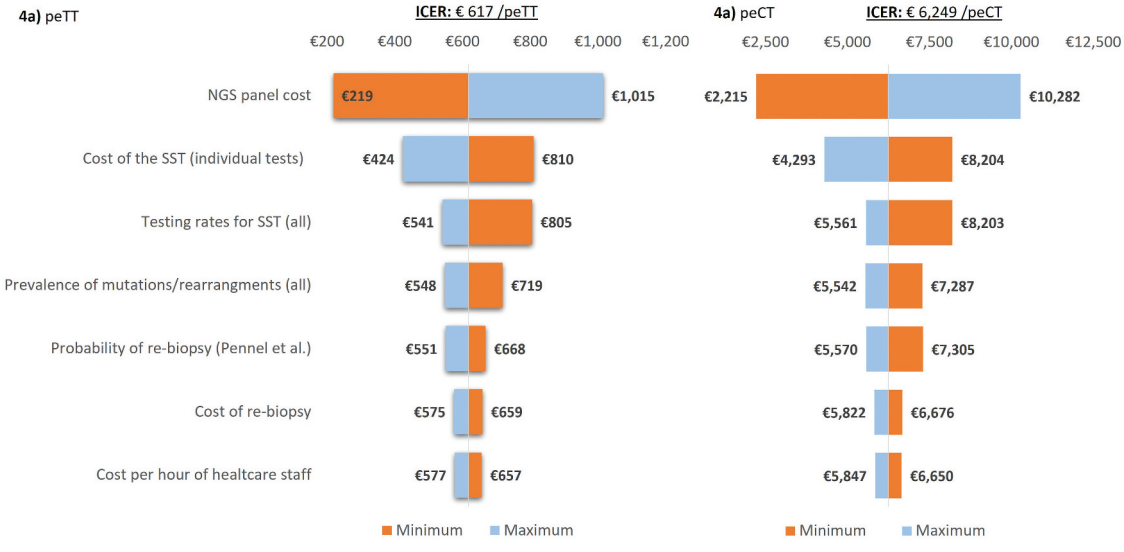

Figure 4. One-way sensitivity analysis, represented by tornado diagrams.

NGS, next-generation sequencing; SST, sequential single testing; ICER, incremental cost-effectiveness ratio; peTT, additional patients eligible for target therapy; peCT, additional patients eligible for enrollment in clinical trials.

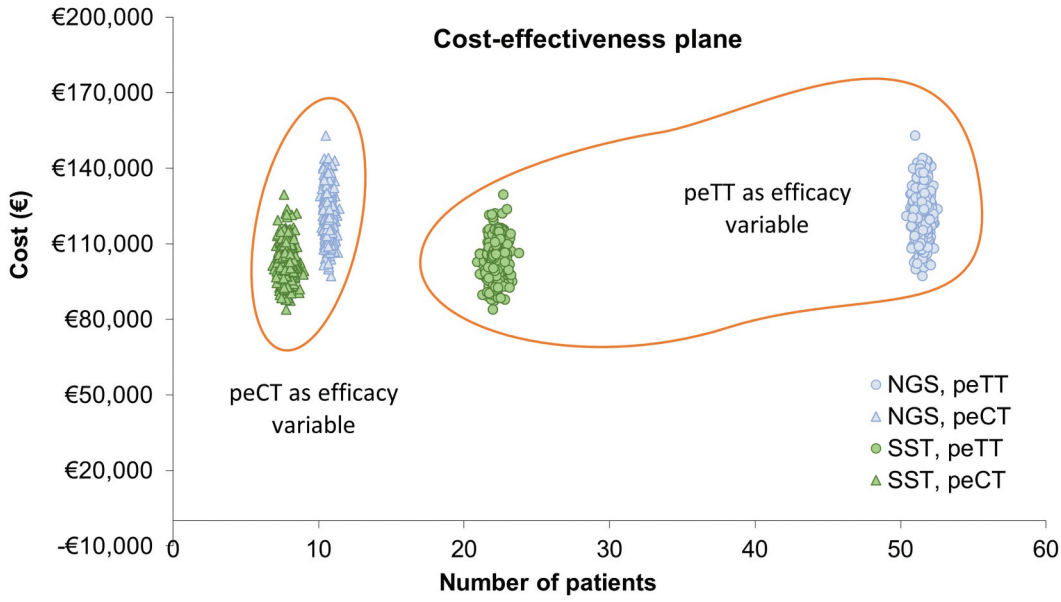

Figure 5. PSA results, represented by a cost-effectiveness scatter plot.

NGS, next-generation sequencing; SST, sequential single testing; peTT, additional patients eligible for target therapy; peCT, additional patients eligible for enrollment in clinical trials.

was assumed that the PD-L1 positivity (TPS >50%) is independent of the detection of alterations in other biomarkers. No published evidence was found to establish a relationship between all the biomarker mutations considered and PD-L1 expression. In the analysis of the LungPath database [13], a correlation was reported between PD-L1 positivity and mutations in EGFR (OR 0.70, p = 0.035) and ALK (OR 1.63, p = 0.084), but since no evidence was available for the other biomarkers, it was agreed to assume independence. Another limitation regarding the time-to-results analysis, is that it does not consider the possible 'batch' effect when several samples are determined by IHC or FISH at the same time in the pathology laboratory. For a more accurate estimation of time-to-results, observational data would be needed.

In the exploratory long-term analysis, there are some important limitations. First, as in all models that use a lifetime time horizon, extrapolations must be made from studies of limited duration. In our study in particular, for some biomarkers targeted therapies are currently in development with efficacy data still immature, so the uncertainty associated with extrapolating their efficacy is even greater. In addition, these targeted therapies currently in development present some uncertainty in terms of cost since the price at which they will be reimbursed is unknown. Also, due to the lack of individualized data for all the treatments considered, and to simplify the model and avoid bias between treatments, the use of exponential models was assumed for the extrapolation of all treatments. In this regard, more mature clinical data will become available in the future to facilitate better extrapolation of survival curves. Finally, in the exploratory long-term analysis treatment-related adverse effects and subsequent treatment costs were not included.

5. Conclusions

In conclusion, our analysis shows that the use of the NGS panel in patients with metastatic NSCLC in the HUVR provides important clinical benefits compared to SST: in the short term, a greater number of patients can be treated with targeted therapies, as more mutation/rearrangement are identified. In addition, this allows more patients to be included in clinical trials targeting certain biomarkers. When comparing these results with the incremental diagnostic cost, the resulting ICER indicates that the NGS panel is a cost-effective strategy. The results of the exploratory long-term analysis seem to confirm the efficiency of NGS when treatment costs are included and LY and QALY are the efficacy variables of the analysis. Considering the new evidence provided by our analysis, a deeper study of the long-term results and the extrapolation of this analysis to the national level is highly recommended.

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Declaration of interest

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Author contributions

All authors contributed substantially to the development of the study. All the authors participated in the design of the analysis. D Carcedo developed the model and wrote the first draft of the manuscript. E de Alava, M Pareja and R Bernabe were the hospital experts who collected and validated data inputs and contributed to results interpretation. All the authors read and approved the final manuscript to be published.

Further information

Roche Farma S.A played no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

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