455

A Predictive Model of the Diagnostic Value of Next Generation Sequencing-Based Genomics Testing in Patients with Metastatic Non-Small Cell Lung Cancer in Spain

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INTRODUCTION

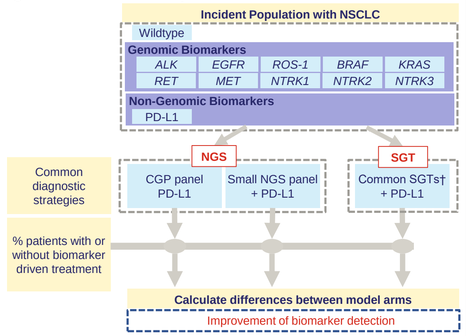
- Cancer is driven by various types of genome alterations, and many of these alterations generate mutant proteins which are the potential foci of targeted anticancer therapies
- Treatment with targeted therapies in cases with actionable driver alterations is recommended to achieve better results in treating advanced and metastatic non-small cell lung cancer (NSCLC)[1]
- Next generation sequencing (NGS) testing may address the limitations in conventional testing practices using single-gene tests (SGTs), as it has seen increasing adoption in Western Europe[2]
- The European Society for Medical Oncology (ESMO) recommends the use of NGS in advanced or metastatic NSCLC for detection of actionable genomic biomarkers[3]
- Currently, payers, health system and laboratory decision makers face uncertainties about potential benefits of broad NGS testing

OBJECTIVE

- To develop an economic model able to assess the potential improvement of biomarker detection using NGS versus combinations of SGTs in a Spanish population with advanced or metastatic NSCLC from a third-party payer perspective (viz. hospital perspective in Spain)

METHODS

Figure 1. Model Concept



CGP = comprehensive gene panel; NGS = next-generation sequencing; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; SGT = single-gene test

METHODS

Model Design

- A dynamic decision tree-based model was developed using Microsoft Excel in the US and adopted for Spain to compare NGS with various combinations of common SGTs (Figure 1)
- The population entering the model was modelled as a cohort to reflect the prevalence of various actionable genomic biomarkers and PD-L1 as a non-genomic biomarker
  - Correlation between genomic biomarkers and PD-L1 was modelled
- NGS strategies included comprehensive gene panels (CGPs) and small NGS panels covering *ALK*, *EGFR*, *ROS-1*, *BRAF*, *KRAS*, *RET*, *MET*, and *NTRK1/2/3*. SGT strategies included multiple SGTs conducted in parallel. All strategies included programmed death-ligand 1 (PD-L1)
- Treatments were assigned per ESMO guidelines[3] for patients with actionable biomarkers (Figure 2)
- Suboptimal treatment was defined as a present but undetected biomarker or detected but with targeted therapy not approved in Spain, leading to the patient not receiving targeted therapy or immunotherapy +/- chemo, as recommended in treatment guidelines
- Patients with true and false negative results for biomarkers were assigned to platinum-doublet chemotherapy (cisplatin + pemetrexed)

RESULTS

- With the application of base-case settings the model predicted that compared with SGT strategies the use of NGS-based diagnostic strategies in patients with advanced or metastatic NSCLC can:
  - Improve detection of actionable biomarkers by relative 51.6%
  - Decrease the proportion of patients initially receiving suboptimal first-line treatment relatively by 25.8% in base case versus 40.6% in alternative scenario (Table 4)

Table 4. Results of Base Case and Alternative Scenario

Outcomes	Diagnostic approach	Base case	Alternative scenario
Percentage of patients with one or more correctly identified actionable biomarkers	NGS	54.7%	54.7%
	SGT	36.1%	36.1%
	Relative change (NGS vs. SGT)	51.6%	51.6%
Number of patients receiving suboptimal treatment (in a cohort of 100,000 patients)	NGS	9,749	11,725
	SGT	13,136	19,731
	Relative change (NGS vs. SGT)	-25.8%	-40.6%

NGS = next-generation sequencing; SGT = single-gene test

CONCLUSIONS

- The current analysis demonstrated that testing strategies with NGS are more comprehensive in the detection of actionable biomarkers and can improve the proportion of patients receiving ESMO recommended therapies, which would be in line with expectations given that test accuracy of NGS is almost uniformly better than SGTs for the more prevalent biomarkers
- The alternate scenario shows that the more targeted therapies are available, the more favourable the results are for NGS
- We conclude that increased NGS availability and testing in Spain versus the current situation with SGTs might result in improved diagnoses and an increased number of NSCLC patients receiving optimal treatments. Access to additional targeted therapies in Spain will further improve these results

Methods

Model Inputs

- The likelihood of correctly diagnosing patients was based on the prevalence of actionable biomarkers (Table 1) as well as sensitivity and specificity of tests (Table 2) which were obtained from published literature and Food and Drug Administration (FDA) summary of safety and effectiveness data
- Diagnostic strategies were based on health care professionals' feedback and published literature (Table 3)
- Given the variability of drug access between Spain and other countries of the European Union, alternative strategies were considered
  - Base case scenario: included only targeted therapies that were approved or available in Spain (for *EGFR*, *ALK*, and *ROS-1* alterations). Patients diagnosed with other genomic biomarkers were assigned to platinum-based chemotherapy (cisplatin + pemetrexed)
  - Alternate scenario: included all targeted therapies with European Medicines Agency (EMA) approval, regardless of their availability in Spain. Therefore, only *KRAS* targeted therapies were excluded

Table 1. Prevalence of Actionable Biomarkers in Patients With NSCLC

Genomic Biomarkers	Prevalence – Biomarkers (%)	Prevalence of PD-L1 ≥ 1% Given Presence of Biomarker (%)
ALK	2.5[3]	55.6[6]
EGFR	15.0[3]	42.3[6]
ROS-1	2.0[3]	85.7[7]
BRAF	2.0[3]	74.0[8]
KRAS	13.0[3]	41.8[9]
RET	2.0[4]	75.0[10]
MET	3.0[4]	63.0[11]
NTRK1	0.12[5]	23.0[12]
NTRK2	0.02[5]	23.0[12]
NTRK3	0.08[5]	23.0[12]
No genomic biomarker detected	60.28[a]	42.1[13]

NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1

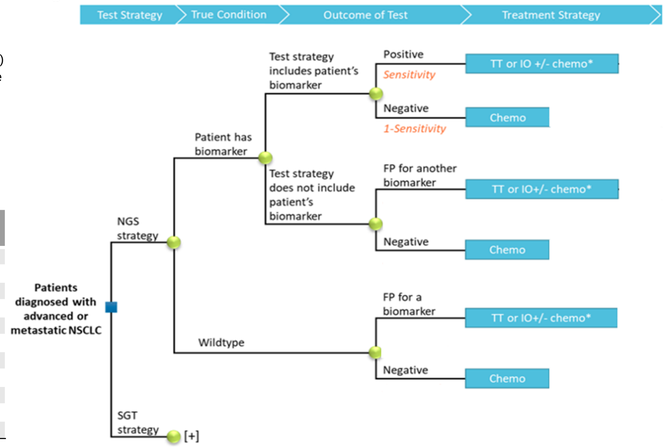
[a]Calculated as one minus the sum of patients with a genomic biomarker

Disclosures

- Gulati A, Goel B, Hesse LM, Jen M-H, Mota A, Molero A and Taipale K are employees of Eli Lilly and Company
- This study model was built by Evidera, funded by Eli Lilly and Company
  - The authors acknowledge Weicheng Ye, Mack Harris and Denise Zou (Evidera, Bethesda, MD, USA) who built the original US model, on which this Spanish adaption is based.
- This study was sponsored by Eli Lilly and Company. Medical writing services were provided by Dr Pooja Sagar (Rx Communications, Mold, UK), funded by Eli Lilly and Company

Methods (cont'd)

Figure 2. Model Structure



FP = false-positive; IO = immuno-oncology agent; M = long-term model; NGS = next-generation sequencing; NSCLC = non-small cell lung cancer; PFS = progression-free survival; SoC = standard of care; TT = targeted therapy

The model only accounted for one testing method for each biomarker to simplify, considering the most used in Spain[3].

Patients could not have more than one actionable genomic biomarker

Note: The calculation follows a decision tree structure where the likelihood of possible outcomes is represented by a node and each potential outcome is represented by a branch. If the patient possesses an actionable biomarker, the probability that the biomarker is detected is based on whether it is tested and the sensitivity of the test. Treatments are assigned following diagnosis

Patients diagnosed with genomic alterations were assigned a targeted therapy, while patients with non-genomic biomarkers, specifically high PD-L1, were assigned an immuno-oncology agent. In the case when a patient is diagnosed with both a genomic alteration and non-genomic biomarker, the genomic alteration takes precedence in determining treatment

Methods (cont'd)

Table 2. Sensitivity and Specificity of Test

Test*	SGT		NGS[a]	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
ALK FISH	90.9[14]	100[14]	100[14]	100[13]
EGFR PCR	94.0[15]	97.7[15]	100[26]	98.4[25]
ROS-1 FISH	100[16, 17]	100[16, 17]	85.0[26]	100[25]
BRAF PCR	97.3[18]	84.6[18]	96.2[26]	97.1[25]
KRAS PCR	97.4[19]	94.6[19]	100[26]	96.8[25]
RET FISH	91.7[20, 21, 22]	100[20, 21, 22]	100[20]	99.6[19]
MET PCR	100[23]	97.4[23]	100[26]	97.8[25]
NTRK1 IHC	96.0[24]	100[24]	84.1[26, 27, 28]	100[25, 26, 27]
NTRK2 IHC	96.0[25]	100[24]	84.1[27, 28]	100[27, 28]
NTRK3 IHC	79.0[24]	100[24]	84.1[27, 28]	100[27, 28]
PD-L1	86.0[25]	92.0[25]	86.0[25]	92.0[25]

CGP = comprehensive genomic profiling; FISH = fluorescence in situ hybridization; IHC: ImmunoHistoChemistry; NGS = next-generation sequencing; PCR = polymerase chain reaction; PD-L1 = programmed death-ligand 1; SGT = single-gene test

*Different testing methods are available for certain biomarkers (e.g., FISH or PCR; DNA or RNA assay). In the model, we only accounted for one method for each biomarker (i.e., FISH or PCR based on DNA sample where applicable) to simplify

[a]Sensitivity and specificity values were assumed to be the same in small NGS panel and CGP

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Methods (cont'd)

Table 3. Testing Strategies

Diagnostic approach	Diagnostic strategy	Details	Estimated Frequency
NGS Strategies	Strategy 1: CGP + PD-L1	• ALK, EGFR, ROS-1, KRAS, BRAF, MET, RET, NTRK1, NTRK2, and NTRK3 • PD-L1 in parallel	20.0%
	Strategy 2: Small NGS panel + PD-L1	• ALK, EGFR, ROS-1, KRAS, BRAF, MET, RET, NTRK1, NTRK2, and NTRK3 • PD-L1 in parallel	80.0%
SGT Strategies	Strategy 1: 1 common SGT + PD-L1	• EGFR • PD-L1 in parallel	10.0%
	Strategy 2: 4 common SGTs + PD-L1	• ALK, EGFR, ROS-1, and BRAF[a] • PD-L1 in parallel	5.0%
	Strategy 3: 3 common SGTs + PD-L1	• ALK, EGFR, and ROS-1 • PD-L1 in parallel	60.0%
	Strategy 4: 2 common SGTs + PD-L1	• ALK and EGFR • PD-L1 in parallel	20.0%
	Strategy 5: PD-L1 only	• PD-L1	5.0%

CGP = comprehensive genomic profiling; NGS = next-generation sequencing; PD-L1 = programmed death-ligand 1; SGT = single-gene test

[a]BRAF is included in the testing strategy for SGT as the biomarker is commonly tested in Spain but no BRAF targeted therapies were included in the base case because they were not reimbursed

Limitations

- Sensitivity and specificity data for specific tests are limited, specifically tests for emerging biomarkers, RNA-based NGS assays, and laboratory developed tests
- In sequence combination of SGT test was not considered, neither the subsequent consequences related to lack of tissue and turn-around times
- Treatment sequence was not modeled, i.e., only first-line treatment and their outcomes were considered

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