

Clinical and Economic Impact of Upfront Next-Generation Sequencing for Metastatic NSCLC in East Asia



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Received 16 November 2021; revised 6 January 2022; accepted 26 January 2022

Available online - 14 February 2022

ABSTRACT

Introduction: Upfront next-generation sequencing (NGS) in patients with metastatic NSCLC has been associated with cost savings and shorter time-to-test results in the United States. Nevertheless, this may not apply in jurisdictions where the prevalence of patients with actionable mutations, cost of health care, and reimbursement models differ.

Methods: A decision analytical model was built to compare sequential, panel, exclusionary, and upfront NGS testing in patients with metastatic NSCLC in Hong Kong. In sequential and panel testing, patients were tested for genomic alterations (GAs) with treatment followed by sequential or NGS. In exclusionary testing, *EGFR* and *ALK* were tested first, followed by NGS. For each modality, the mutation identified, time to receive testing results, and costs (2020 U.S. dollars) were estimated.

Results: Exclusionary testing required the shortest time-to-results (1.6 wk) and was most cost saving. In the scenario where all patients used exclusionary testing, a cost saving of \$4.6 million was expected relative to current practice, with 90.7% of actionable and 46.5% of nonactionable GAs detected; when all patients used NGS, it would be \$2.9 million more expensive with a 100% GA detection rate. Results were sensitive to testing costs and the proportion of patients that continued testing.

Conclusions: Exclusionary testing is the best option in terms of cost and time-to-results in Hong Kong. This finding

may be applicable for other Asian countries; however, exclusionary testing does not capture all possible GAs. As more GAs become actionable and the cost of NGS declines, NGS may become a cost-saving option.

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Disclosure: Dr. Loong reports receiving funding from Novartis Pharmaceuticals, AbbVie, Bayer, Eisai, Eli Lilly, Guardant Health, Boehringer Ingelheim, Celgene, Illumina, Merck Sereno, Takeda, and George Clinical. Chan and Chang are employees of Novartis Pharmaceuticals Corporation, Hong Kong. Dr. Zhou and Ms. Tang are employees of Analysis Group, Inc., a consulting firm that received financial support from Novartis Pharmaceuticals for the conduct of this study. Ms. Gibbs is an employee of Novartis Pharmaceuticals Corporation, Dubai, United Arab Emirates. Dr. Wong declares no conflict of interest.

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Cite this article as: Loong HH, Wong CKH, Chan CPK, et al. Clinical and economic impact of upfront next-generation sequencing for metastatic NSCLC in East Asia. *JTO Clin Res Rep*. 2022;3:100290.

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ISSN: 2666-3643

<https://doi.org/10.1016/j.jtocr.2022.100290>

Keywords: Metastatic NSCLC; Next-generation sequencing; Genomic alteration; Economic impact; East Asia

Introduction

Lung cancer is the leading cause of cancer mortality in the world, with East Asia bearing the greatest proportion of this burden. In 2018 alone, 45% of the world's new lung cancer cases and 46% of worldwide deaths from lung cancer occurred in East Asia.¹ Genomic studies in NSCLC, the most common type of lung cancer,² have identified the presence of genomic alterations (GAs) in a number of driver oncogenes that cause signaling proteins to abnormally activate cancer cell proliferation and survival.³ Development of targeted therapies that specifically act on pathways associated with these NSCLC driver oncogene alterations has led to substantial improvements in treatment response and progression-free survival rates in patients with advanced or metastatic NSCLC (mNSCLC).⁴⁻⁶ Thus, the standard of care for mNSCLC in patients harboring tumors with GAs has been transformed in recent years from chemotherapy to personalized targeted therapy.^{3,7,8}

In Asia, guidelines for the management of patients with mNSCLC currently recommend the use of targeted therapies acting on driver oncogene alterations in *EGFR* (erlotinib, gefitinib, afatinib, osimertinib), *ALK* (crizotinib, ceritinib, alectinib), *ROS1* (crizotinib), and *BRAF* V600E (trametinib and dabrafenib), including programmed cell death protein-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors (e.g., nivolumab, pembrolizumab, atezolizumab), across various lines of treatment for mNSCLC.⁹ Targeted therapies acting on driver oncogene alterations in *MET* (e.g., tepotinib, capmatinib) and *RET* (e.g., pralsetinib) have recently entered the Asian market or will be available in the near future.¹⁰⁻¹² To allow for prompt selection of the most appropriate targeted treatment, and hence improve survival rates, it is crucial to identify these oncogenic drivers in patients with NSCLC at diagnosis through molecular testing.^{4,13} Routine testing for *RET* rearrangement or *MET* exon 14 skipping mutation is also expected to be performed as these newer targeted therapies become more widely available. Nevertheless, despite the current recommendations and continued addition of new targeted therapies, the rate of molecular testing, including single-gene testing, in East Asian patients with NSCLC varies considerably, from as low as 42% in Mainland China to 91% in Taiwan, meaning many patients are not receiving optimal treatment.¹⁴ Thus, there remains a considerable need to improve the implementation of efficient and cost-saving molecular testing strategies in East Asian clinical practice to

meet guideline recommendations and ultimately improve patient survival. With ongoing clinical trials of targeted therapies for NSCLC driver oncogene alterations in *KRAS* G12C, *NTRK* fusions, and *HER2*, coupled with a continuing rise in the identification of other potential oncogene targets, molecular testing will be important, as is determining an optimal molecular testing strategy.

Currently, diagnostic testing strategies used to identify GAs in NSCLC include simple single-gene testing, hotspot panels, and more recently next-generation sequencing (NGS).¹⁵ For single-gene testing strategies in Asia, generally the most common actionable alterations with access to associated targeted therapies (e.g., *EGFR* inhibitors, *ALK* inhibitors) are being tested first. Patients who tested negative would have to continue testing for other GAs in sequence.¹⁵ Consequently, finding actionable oncogenic alterations by means of single-gene testing can be inefficient and time-consuming, especially considering the expanding number of oncogene targets. In many cases, patients do not get the opportunity to proceed with the next GA test after the initial exclusionary testing (e.g., *EGFR*, *ALK*) given the urgency to receive cancer treatment. Furthermore, because most NSCLC is diagnosed at an advanced stage,¹⁶ the ideal time for surgical resection has already passed and often only a small biopsy or cytology samples are attainable.¹⁵ This results in many patients either requiring invasive, inconvenient, and costly rebiopsies or having insufficient sample available to conduct further molecular testing.^{15,17,18}

Hotspot panel, in contrast, focuses on simultaneously testing several known GAs that correspond with approved targeted therapies.¹⁵ Nevertheless, negative results using this method generally require follow-up with single-gene tests or NGS to identify less common alterations, again leading to an increase in time, inconvenience, and costs.¹⁵

Upfront NGS is a fast and effective mutation testing modality that allows concurrent screening of numerous gene alterations in a single test.^{15,19} A previous study on the economic impact of NGS testing in newly diagnosed mNSCLC in the United States found that upfront NGS was associated with substantial cost savings and the same or shorter time-to-test results compared with sequential single-gene testing or exclusionary strategies and hotspot panel testing.²⁰ Nevertheless, the positioning and economic implications of upfront NGS in the East Asian market could be quite different especially given the notable disparities in NSCLC mutation epidemiology between East Asian and Western populations.²¹⁻²³ For example, *EGFR* mutations are found in approximately 40% to 60% of lung adenocarcinomas in East Asia

compared with only 10% to 20% of lung adenocarcinomas in Western countries.^{4,24–27} Considering this, it is particularly important to evaluate the efficacy and economic value of upfront NGS versus other testing modalities in East Asia to determine whether NGS is the most cost-saving strategy in the first-line setting.

Using Hong Kong as an example, this study aimed to evaluate the economic impact of upfront NGS versus other testing modalities in East Asian patients with mNSCLC. A decision analytical model was developed with inputs that reflect the Hong Kong market to estimate differences in costs, time to appropriate therapy, and proportion of patients with actionable/non-actionable alterations between upfront NGS, exclusionary (i.e., single-gene testing for *EGFR* and *ALK*, followed by NGS to continue testing for other mutations), single-gene sequential, and hotspot panel testing modalities. We also conducted a budget impact analysis to evaluate the financial impact of adapting upfront NGS from the Hong Kong payer’s perspective.

Materials and Methods

Model Overview

We developed a decision analytical model using Microsoft Excel 2016 to compare costs and outcomes associated with different testing modalities from a Hong

Kong Hospital Authority’s perspective. The model structure, as illustrated in Figure 1, was modified from the model used by Pennell et al.²⁰ to reflect current practice in Hong Kong as confirmed by clinicians. The testing population included adult patients in Hong Kong with newly diagnosed mNSCLC with unknown mutation/rearrangement status. The model considered *EGFR*, *ALK*, *ROS1*, *BRAF* V600E, *RET*, *MET*, *HER2*, and *KRAS* G12C alterations, *NTRK* fusions, and PD-L1 overexpression on the basis of clinical trials on emerging targeted therapies.²⁸ GAs were considered to be actionable, such as those with treatments approved or to be approved soon in Hong Kong (*EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, *RET*), or nonactionable, such as those with no Hong Kong-approved treatments (*KRAS* G12C, *NTRK* fusions, *HER2*).²⁹ The current study referred to actionable and nonactionable GAs on the basis of approved treatments in Hong Kong, though targeted treatments have been approved for certain nonactionable GAs (e.g., *KRAS* G12C) in other countries. The model assumed that the initial biopsy taken at mNSCLC diagnosis to have been incurred in all patients, and the cost was not considered. Testing costs for nonactionable alterations were assumed to be covered in clinical trials and thus not incurred in the current model.

We ascertained the mNSCLC GA status of patients in the testing population after one of the four testing

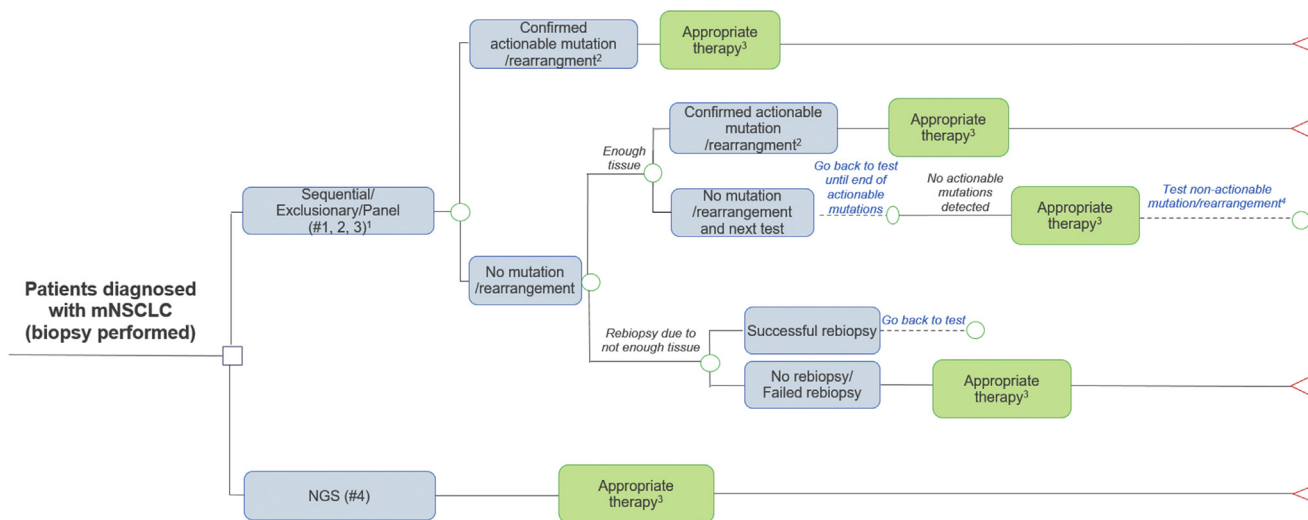


Figure 1. Decision tree. ¹For each testing strategy #1 to #3 sequential, exclusionary, and hotspot panel, detailed testing specifications are outlined in the Materials and Methods section (model overview). ²Actionable mutations/rearrangements considered are *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, and *RET*. Nonactionable mutations/rearrangements considered are *KRAS* G12C, *NTRK1*, and *HER2*. It is assumed that patients who tested positive for these nonactionable mutations/rearrangements may be considered eligible for clinical trial for post-first-line care. ³Appropriate therapy is considered anticancer treatment deemed appropriate by the care provider given their assessment of the patient, including the results of the genomic testing. Appropriate therapy may include but is not limited to chemotherapy, immunotherapy, and targeted therapy. ⁴Patients who receive appropriate therapy and have tested negative for actionable mutations/rearrangements may continue testing for nonactionable mutations/rearrangements to be considered for clinical trial eligibility for post-first-line care. Among those who continue, patients without enough tissue may receive rebiopsy. #, number; mNSCLC, metastatic NSCLC; NGS, next-generation sequencing.

	Actionable alterations							Nonactionable alterations			NGS
	PD-L1	EGFR	ALK	ROS1	BRAF	MET	RET	KRAS G12C	NTRK1	HER2	
Sequential ¹	1st	1st	1st	2nd	3rd	4th	5th	6th	7th	8th	6th
Exclusionary ²	1st	1st	1st	X	X	X	X	X	X	X	2nd
Hotspot Panel ¹	1st	1st	1st	1st	1st	1st	1st	2nd	3rd	4th	2nd
NGS	1st	X	X	X	X	X	X	X	X	X	1st

Figure 2. Testing modalities. ¹A total of 25% of patients who tested negative for actionable alterations using either the sequential or hotspot modalities continued with single-gene sequential (12.5%) or NGS (12.5%) tests to identify nonactionable genomic alterations (*KRAS* G12C, *NTRK1*, *HER2*). Single-gene tests were assumed to be only ordered successively after receiving a negative result for the previous test. ²A positive test result for *EGFR* or *ALK* alterations in the exclusionary modality precluded further tests. Of the patients, 25% who tested negative for both *EGFR* and *ALK* alterations were assumed to be tested for remaining actionable plus nonactionable genomic alterations using NGS. NGS, next-generation sequencing; PD-L1, programmed death-ligand 1.

modalities outlined in Figure 2. In sequential or exclusionary testing, simultaneous testing of *EGFR* and *ALK* is the first step to identify the most prevalent alterations.

Patients who tested negative and had sufficient tissue sample continued with testing for the next actionable alteration in the sequential single-gene testing modality, whereas a proportion of patients would continue with NGS under the exclusionary modality. Hotspot panel modality included a panel of simultaneous testing for all actionable GAs (*EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, *RET*), and the upfront NGS covered all possible GAs for NSCLC in one test. Patients also received initial PD-1/PD-L1 screening at diagnosis, alongside the first test in a given modality.

For sequential single-gene or hotspot panel testing modalities, of patients who tested negative for actionable GAs, 25% were assumed to continue with nonactionable alteration testing (12.5% with sequential testing and 12.5% with NGS). For exclusionary testing, of the patients who tested negative for *EGFR* and *ALK*, 25% were assumed to continue testing with NGS. In a scenario analysis, 100% were assumed to continue testing for sequential single-gene, hotspot panel testing, or exclusionary modalities.

After the initial test, 8% of patients were assumed to need a rebiopsy to continue with each additional testing, but only 30% of patients who needed a rebiopsy actually received it. The model assumed that

all tests were 100% accurate with no test sensitivity or specificity considered and that *MET* tests were able to detect both rearrangements and exon 14 skipping mutations.

Model Inputs

Epidemiology data used to estimate the size of a cohort of adults (≥ 18 y) with mNSCLC in Hong Kong are summarized in Table 1. The model assumed a total of 4094 adults diagnosed with having mNSCLC in a given year, on the basis of the total population in Hong Kong, derived from the 2016³⁰ Hong Kong Census, and estimates of lung cancer, NSCLC, and metastatic disease prevalence.^{2,16,31} The estimated rates for each GA in Hong Kong in the modeled population are also listed in Table 1.

Cost parameters including initial PD-1/PD-L1 screening, single-gene tests, NGS, and rebiopsy are listed in Table 2. The unit costs for testing were obtained from The Chinese University of Hong Kong University Pathology Service 2019 testing manual, Hong Kong Molecular Pathology Diagnostic Centre 2019 test catalog, Sanomics Limited (data on file, Novartis), and ACT Genomics (data on file, Novartis). We calculated the total costs for each testing modality by multiplying the unit cost of testing by the number of patients receiving each test, which was ascertained from rebiopsy and continued testing rates. The focus of

Table 1. Epidemiology, Population, and Alteration Rate Inputs

Variables	Population		Source
Patient population with mNSCLC	Input value, %	Calculated, n	
Hong Kong population, n	—	7,336,585	Hong Kong census, 2016 ³⁰
Adults (≥18 and <65 y)	70	5,157,722	Hong Kong census, 2016 ³⁰
Adults (≥65 y)	16	1,163,153	Hong Kong census, 2016 ³⁰
Adults (≥18 and <65 y) with lung cancer	0.08	3877	NCI SEER ³¹
Adults (≥65 y) with lung cancer	0.80	9356	NCI SEER ³¹
Patients with lung cancer with NSCLC	89	11,740	Yang et al. 2005 ²
Patients with metastasis with NSCLC	35	4094	Yang et al. 2005 ²
NSCLC alteration rates	Input value, %		
<i>PD-L1</i>	22.0		Dietel et al. 2019 ³⁹
<i>EGFR</i>	26.2		Tong et al. 2016 ²⁷
<i>ALK</i>	3.9		Tong et al. 2016 ²⁷
<i>ROS1</i>	1.5		Tong et al. 2016 ²⁷
<i>BRAF</i>	2.8		Lin et al. 2019 ⁴⁰
<i>MET exon 14 skipping</i>	2.6		Tong et al. 2016 ²⁷
<i>RET</i>	1.4		Wang et al. 2012 ⁴¹
<i>KRAS G12C</i>	4.3		Loong et al. 2020 ⁴²
<i>NTRK1</i>	0.3		Ling 2018 ⁴³
<i>HER2</i>	2.4		Song et al. 2016 ⁴⁴
<i>BRAF V600E</i>	31% of <i>BRAF</i> mutations		Lin et al. 2019 ⁴⁰

mNSCLC, metastatic NSCLC; NCI SEER, National Cancer Institute Surveillance, Epidemiology, and End Results; PD-L1, programmed death-ligand 1.

Table 2. Model Inputs

Parameters	Value	Source
Costs (2020 USD)		
PD-1/PD-L1	218	Sanomics (data on file, Novartis), UPS
Single-gene tests for actionable alterations ¹		
<i>EGFR</i>	556	UPS
<i>ALK</i>	281	UPS, HKMPDC
<i>ROS1</i>	549	UPS, HKMPDC
<i>BRAF</i>	376	UPS, HKMPDC
<i>MET</i>	453	UPS, HKMPDC
<i>RET</i>	527	UPS, HKMPDC
NGS	3222	Sanomics (data on file, Novartis), UPS, ACT Genomics (data on file, Novartis), HKMPDC
Rebiopsy	2859	Expert clinical opinion
Rebiopsy inputs		
Patients who need rebiopsy after each test	8%	Vanderlaan et al. 2014 ⁴⁵
Patients who received rebiopsied after each test (of those in need)	30%	Expert clinical opinion
Patients who failed rebiopsy (of each rebiopsy attempted)	15%	Handorf et al. 2012 ⁴⁶
Time to receive rebiopsy	3.0 wk	Expert clinical opinion
Time inputs for tests		
Time to receive results for single-gene tests	1.5 wk	Expert clinical opinion
Time to receive results for multiple-gene panel	2.0 wk	Expert clinical opinion
Time to receive results for NGS	2.0 wk	Expert clinical opinion

Note: All costs were converted to 2020 USD from HKD using a prevailing exchange rate obtained from the Linked Exchange Rate System in Hong Kong (1 USD = 7.8 HKD) on the basis of Hong Kong Monetary Authority. Fees and Charges. https://www.ha.org.hk/visitor/ha_visitor_index.asp?Content_ID=10045&Lang=ENG. HKMPDC, Hong Kong Molecular Pathology Diagnostic Centre; HKD, Hong Kong dollar; NGS, next-generation sequencing; PD-1 programmed cell death protein-1; PD-L1, programmed death-ligand 1; UPS, University Pathology Service; USD, U.S. dollar.

the model was on genomic testing-related costs, and therefore, costs of treatment or other aspects of mNSCLC care (e.g., monitoring, costs associated with treating adverse events) were not considered in the model. All costs were reported in 2020 U.S. dollars.

Inputs for rebiopsy and time to receive test results are detailed in Table 2. The time to receive test results was assumed to be 1.5 weeks for each of the single-gene tests and 2.0 weeks for both hotspot panel and NGS. If a rebiopsy was needed, the time to receive rebiopsy results was 3.0 weeks. We assumed that patients would start appropriate therapy as soon as they received the test results for actionable alterations.

Model Outputs

We evaluated the following three model outputs for each testing modality: (1) total testing-related costs, (2) time to appropriate therapy for actionable alterations, and (3) proportion of patients identified with actionable/nonactionable GAs. The difference in total costs between each testing modality versus NGS and each testing modality versus exclusionary was estimated. One-way sensitivity analyses were conducted to evaluate the robustness of the model results with regard to the total cost difference between NGS and other testing modalities by varying key model parameters once at a time. Limits for the model parameters were set at plus or minus 25% of the base-case values.

Budget Impact Analysis

On the basis of the market size and testing-related costs for each modality, the total budget impact of increasing exclusionary testing or upfront NGS to 100% in a given year was estimated from the Hong Kong payer perspective. The current market share of each testing

was assumed to be 15% for upfront NGS, 65% for sequential testing, 5% for exclusionary testing, and 15% for hotspot panel on the basis of clinical opinion. In addition, two scenario analyses were conducted to determine the break-even price of NGS in order for the upfront NGS to be cost saving. This allowed us to evaluate potential future scenarios where NGS test costs decrease as a result of advancing technology and an increase in the volume of testing. In another scenario analysis, we evaluated the budget impact when assuming all the GAs are actionable in the current model. This scenario allowed us to evaluate the impact of an increase in the volume of testing in the future.

Results

Total Testing-Related Costs and Time to Appropriate Therapy

In our model, using the current costs of NGS and single-gene tests in Hong Kong, exclusionary testing at a total cost of \$6,535,487 was found to be the cheapest among the four testing modalities. NGS at a total cost of \$14,082,194 was the most expensive option (Fig. 3). Exclusionary testing represented total cost savings of \$3,871,105 versus sequential, \$6,618,285 versus hotspot panel, and \$7,546,707 versus NGS. When the proportion of patients who continued testing increased from 25% to 100%, we found that exclusionary testing remained cheaper than hotspot panel and NGS but would be more expensive compared with sequential.

When the total number of individual tests received, the time of each test, and the time for rebiopsy were taken into account, exclusionary testing yielded the shortest time to appropriate therapy for actionable alterations at 1.6 weeks (Fig. 3), which was 0.4 weeks

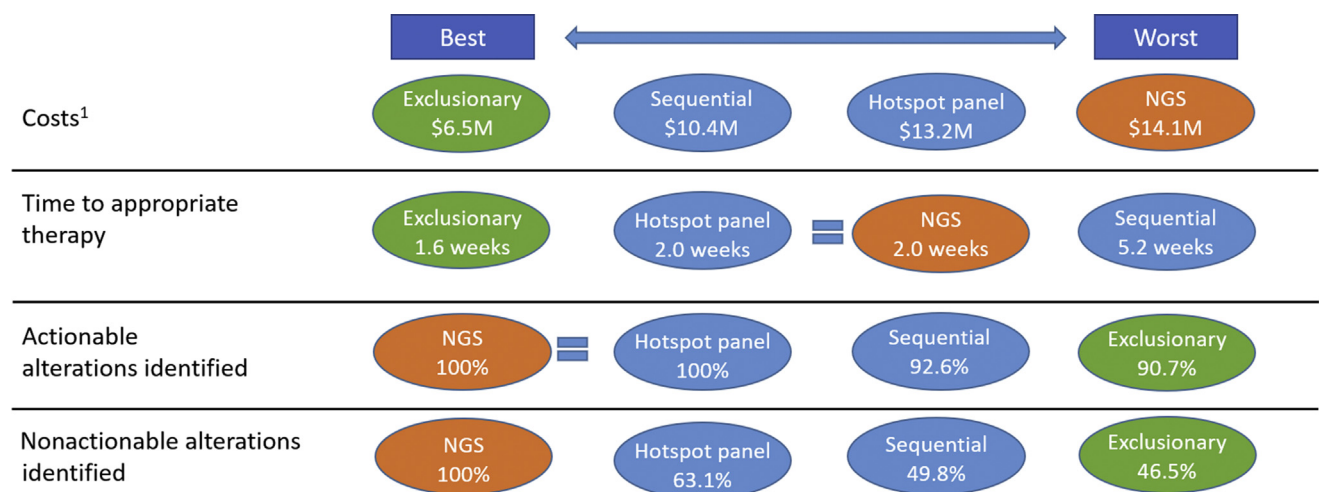


Figure 3. Base-case results. ¹Values reported in 2020 U.S. dollars. M, million; NGS, next-generation sequencing.

faster than hotspot panel and NGS and 3.6 weeks faster than sequential testing.

Proportion of Patients With Actionable/Nonactionable GAs

Both NGS and hotspot panel testing identified 100% of patients with actionable GAs. Exclusionary testing identified the lowest proportion of patients with actionable GAs at 90.7%, followed by sequential testing at 92.6% (Fig. 3). In addition to identifying all patients with actionable alterations, NGS identified all patients with nonactionable alterations who were eligible for enrollment in clinical trials of novel treatments, followed by hotspot panel at 63.1% of patients. Nevertheless, sequential and exclusionary testing identified less than half of patients with nonactionable alterations (Fig. 3).

One-Way Sensitivity Analyses

Results from the one-way sensitivity analyses revealed that total cost differences between NGS and other testing modalities were robust to variations in model inputs. Among the varied inputs, total cost differences were found to be most sensitive to variations in NGS cost, single-gene test costs, and the proportion of patients that continued to nonactionable testing and were less sensitive to variations in inputs related to rebiopsy costs.

Budget Impact Analysis

On the basis of the current market share, the testing-related costs were \$11,176,454 for all adults diagnosed with having mNSCLC in a given year ($n = 4094$), equivalent to \$2730 per diagnosed patient per year. If Hong Kong adopted 100% use of exclusionary testing, the total testing-related costs decreased to \$6,535,487, resulting in a cost saving of \$4,640,967 per year or \$1134 per diagnosed patient per year. In the scenario analysis, where the proportion of patients who continue testing was 100%, we found that exclusionary testing remained cost saving.

Conversely, if 100% testing were on the basis of upfront NGS, the total testing-related costs increased to \$14,082,194, costing the payer an additional \$2,905,740 per year or \$710 per diagnosed patient per year. The scenario analysis revealed that upfront NGS became cost saving compared with the status quo when the cost for NGS was discounted by 28% (i.e., NGS cost equals to \$2320). In addition, when assuming all GAs are actionable in the current model, NGS could be cost saving with a discount of 5.5% (i.e., NGS cost equals to \$3044).

Discussion

Using Hong Kong as an example, we developed an economic model to identify the most efficient and cost-saving molecular testing strategy for use in East Asia. Our model reveals that the proposed exclusionary testing method (i.e., single-gene testing for *EGFR* and *ALK*, followed by NGS to continue testing for other alterations) led to substantially lower costs and shorter time to appropriate therapy in patients with mNSCLC compared with sequential, hotspot panel, and upfront NGS testing modalities. This is contrary to the findings suggested by Pennell et al.,²⁰ who identified an upfront NGS approach being the most cost saving in the United States. This is mainly owing to the notable disparities in NSCLC mutation epidemiology between East Asian and Western populations in terms of *EGFR* and *ALK* alterations. On the basis of our model, positioning NGS after *EGFR* and *ALK* testing would be an attractive testing strategy to adopt given its economic savings versus the current approach using sequential testing strategies.

Although NGS is being adopted in Hong Kong, it is not currently reimbursed and there remains a lack of awareness of the benefits of this emerging technology.³² Nevertheless, the emergence of new NGS testing facilities and commercialization of such platforms across Asia and the rest of the world is indicative of its increasing use in clinical practice. This will inevitably lead to more favorable price adjustments for NGS to the consumer.³³ Coupled with the expected increase in the identification of relatively rare actionable GAs and expansions in the availability of targeted therapies³⁴ specific to these alterations, a molecular testing methodology that necessitates a wider testing bandwidth that can be performed concurrently is highly desired. Thus, there is potential for NGS to become a cost-saving alternative in the first-line setting compared with other testing paradigms in the near future. This possible outcome was substantiated by one of the scenarios explored in the budget impact analysis, which revealed that cost savings could be achieved if the price of NGS testing was reduced to \$2320. In addition, when assuming more GAs are actionable, cost savings could be achieved with NGS with a lower price discount (i.e., NGS cost equals to \$3044).

Although sequential single-gene testing, exclusionary testing, and hotspot panel testing are currently cheaper options compared with upfront NGS, not all alterations would be identified using these methods, meaning some patients may not receive optimal treatment. This issue was highlighted in an analysis by Drilon et al.,³⁵ in which patients with lung adenocarcinomas underwent testing with NGS after having previously tested negative for GAs by means of non-NGS methods. Of the patients who underwent further testing with NGS, 26% were found to

have actionable GAs and 39% were found to have GAs that made them eligible for enrollment in a clinical trial.³⁵ Similarly, our study revealed that upfront NGS was able to identify 37% to 53% more patients with nonactionable alterations than the other testing modalities. With the number of regulatory approvals for targeted therapies increasing and ongoing research establishing progressively more actionable GAs (e.g., *KRAS* G12C, *NTRK* fusions, and *HER2*), the ability to capture all patients with actionable and nonactionable alterations quickly and effectively is becoming increasingly important.

The current model reflects the Hong Kong market; however, similarities in driver mutation epidemiology in East Asian countries indicate that the model can be used to represent patients with mNSCLC throughout East Asia.²⁶ A recent study evaluating NGS and other testing strategies in Singaporean patients with NSCLC concluded that upfront NGS is feasible and cost saving compared with standard sequential testing, although it is more expensive than a strategy testing *EGFR* only followed by NGS.³⁶ Their findings are similar to our model results in an *EGFR* mutant-predominant patient population, though the difference in model assumptions and inputs (e.g., NGS unit cost) reflected the variations across the local markets in East Asia.

The results from our costs and time to appropriate therapy analyses contrast the model developed by Pennell et al.²⁰ from the perspective of U.S. payers, in which upfront NGS testing yielded substantial cost savings and shorter time-to-test results compared with other testing modalities. The disparity between our model and Pennell et al.²⁰ was mainly influenced by differences in the epidemiology of driver alterations between populations with NSCLC in Asia and the United States and thus the alterations chosen for testing in the exclusionary modality. In our Hong Kong model, *EGFR* and *ALK* alterations were simultaneously tested in the exclusionary modality because they were the most prevalent actionable alterations accounting for 30% of patients with mNSCLC.²⁷ In contrast, *EGFR* and *ALK* alterations accounted for only 19% of patients with mNSCLC in the U.S. model, and thus, the *KRAS* mutation, the most prevalent alteration accounting for 25% of patients with mNSCLC, was tested in the U.S. exclusionary modality.²⁰ Therefore, our model was capable of capturing more patients using the exclusionary modality than the U.S. model. In our model, fewer patients in the exclusionary modality proceeded to further testing and rebiopsy, resulting in shorter time-to-treatment and cost savings compared with the U.S. model. The cost savings could also be partially owing to the fact that the rebiopsy unit cost was higher compared with the U.S. model. In the current model, the rebiopsy unit cost was calculated on

the basis of a more comprehensive method, which counted for not only the cost of the procedure but also any additional costs associated with admission, blood tests, and routine chest radiography. Nevertheless, with the increasing applications of liquid biopsy as an alternative to the classic tissue biopsy,³⁷ use of liquid biopsy may be considered in the future analysis. On a different note, *EGFR* and *ALK* alterations are actionable—patients captured in the exclusionary modality in our model would go onto receive targeted treatment and those who tested negative can be qualified for immunotherapy or chemotherapy, whereas the *KRAS* mutation was nonactionable, and thus patients captured in the U.S. exclusionary model would go on to receive conventional chemotherapy treatment. This model reveals the potential clinical and economic significance of positioning NGS after *EGFR* and *ALK* reflexive testing, which have already been routinely incorporated into clinical practice. Given the high testing rates and volume of *EGFR* and *ALK* tests, many laboratories have adopted laboratory-developed tests and in vitro diagnostics, resulting in relatively inexpensive reflexive testing methods with quick turnaround time. If a payer decides to reimburse NGS for *EGFR*- and *ALK*-negative patients, our model reveals that there are already cost savings being realized by adopting NGS after reflexive *EGFR* and *ALK* tests, which can continue to capture all actionable alterations that have associated regulatory approved targeted therapies.

As with any economic evaluation, there are limitations to our study. First, the model did not consider costs other than testing and rebiopsy costs. The full economic impact from the payer perspective of each testing modality during the whole disease journey, including treatment costs and monitoring costs, was not reflected in the results. The current model focused on the evaluation of the most efficient and cost-saving molecular testing strategy. Nevertheless, the impact of genomic sequencing with regard to the clinical benefit of receiving targeted therapy and downstream medical care costs should be considered in future economic assessments to provide a full picture of the economic and clinical impact. Second, most of the NSCLC alteration rate inputs used in our decision tree model were collected from Hong Kong, which may not be fully representative of all patients with mNSCLC in East Asia. Although Hong Kong is regarded as an international city, it has a predominant and homogenous ethnic Chinese population accounting for more than 92% of its residents. Within East Asia, there are various countries and regions that are populated with more diverse ethnicities. Nevertheless, Liam et al.³⁸ have previously reported on the prevalence of *EGFR* mutations in Malaysian cohorts, which consisted of Chinese (40.8%), Malay (37.2%), and Indian (33.3%) patients. In these cohorts, the frequency

of *EGFR* mutations was not significantly different in patients across these three ethnic groups. This indirectly suggests that molecular epidemiologic distribution of NSCLC-associated alterations from a more homogenous East Asian ethnic population may be considered generalizable for the entire region. Finally, as the model inputs reflect the Hong Kong market, the costs in the model were from the Hong Kong Hospital Authority perspective and may not be generalizable to other payers within East Asia or beyond. To evaluate the diagnostic modalities best suited to help patients with mNSCLC receive timely targeted treatment in other markets, we recommend equivalent evaluations be performed with input parameters tailored to each locality.

In conclusion, contrary to the findings by Pennell et al.,²⁰ exclusionary rather than upfront NGS is the best option in terms of costs and time to appropriate therapy under the current scenario in Hong Kong. This outcome is mainly influenced by the higher prevalence of patients with mNSCLC with *EGFR* mutations in East Asian populations versus Western populations, which can be readily detected by single-gene tests. Exclusionary testing, however, does not capture all possible GAs. As more GAs become actionable, such as *KRAS* G12C, *NTRK* fusions, and *HER2*, and the costs of NGS testing decreases, NGS may become a cost-saving option.

CRedit Authorship Contribution Statement

Herbert H. Loong, Catherine P. K. Chan, Andrea Chang, Meaghan Gibbs: Conceptualization, Study design.

Wenxi Tang, Zheng-Yi Zhou: Formal analysis.

Herbert H. Loong, Carlos K. H. Wong, Catherine P. K. Chan, Andrea Chang, Zheng-Yi Zhou, Wenxi Tang, Meaghan Gibbs: Data interpretation, Writing - review and editing.

Acknowledgments

This work was supported by Novartis Pharmaceuticals, Hong Kong. Medical writing assistance was provided by Heidi Eriksen, who was a contractor of Analysis Group, Inc. and analytical support was provided by Honghao Fang, who is an employee of Analysis Group, Inc.

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