Cost-utility analysis of *EML4-ALK* fusion testing followed by treatment with crizotinib in patients with Non-Small Cell Lung Cancer (NSCLC)

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ABSTRACT

Objective

NSCLC is the most common type of lung cancer and accounts for about 85% of all lung cancers. Currently a majority of patients with NSCLC are treated with surgical resection and/or cytotoxic drugs. Chemotherapy has resulted in a modest increase in the overall survival of patients (median survival of 8 months with chemotherapy vs median survival of 5.7 months for patients without chemotherapy). Advances have been made in understanding the molecular mechanisms of lung cancer. The discovery of new biomarkers, driver mutations and signaling pathways in NSCLC has changed the treatment strategy for patients with NSCLC.

'Targeted therapies' or 'personalized medicine' in NSCLC include testing the tumor for the genetic mutations and tailoring the treatment against specific mutations found in the tumor. Success in targeted therapies has been achieved for a small sub-set of NSCLC patients who harbor specific mutations.

In 2012, Profile 1007, a phase 3 randomized trial by Pfizer, Inc. demonstrated that crizotinib (Xalkori, Pfizer, Inc.) offers significant improvement in clinical outcomes as a second line therapy for the treatment of *EML4-ALK* fusion–positive non-small-cell lung cancer (NSCLC). In 2013, the US Food and Drug Administration (FDA) approved crizotinib for the treatment of patients with metastatic NSCLC whose tumors are *EML4-ALK* fusion positive as detected by the Vysis *ALK* Break Apart FISH Probe companion diagnostic test (Abbott Molecular). In this paper, we have conducted a cost-utility analysis of *EML4-ALK* fusion testing of NSCLC patients with the FDA approved companion diagnostic test.

Methods

We constructed a Markov model to conduct a cost-utility analysis from a health care sector perspective. We used a lifetime horizon (10 years) in patients with metastatic NSCLC, who had received one prior platinum-based regimen. Utility values and probabilities for the model were obtained from the literature and the drug costs were obtained from 2013 Medicare Drug Fee Schedule.

Results

EML4-ALK testing with the Vysis *ALK* Break Apart FISH Probe diagnostic test in a population of metastatic NSCLC patients resulted in an incremental health gain of 0.4055 quality-adjusted life years (QALYs) compared with no molecular testing. Testing for *EML4-ALK* fusion mutations resulted in an increased cost of USD 56,938. The incremental cost effectiveness ratio (ICER) was USD 140,414 per QALY gained. The major driver of ICER was the low prevalence of *ALK* rearrangements in the population of NSCLC patients and the cost of crizotinib.

Conclusion

Overall, this analysis suggests that *EML4-ALK* testing with the Vysis *ALK* Break Apart FISH Probe diagnostic test in a population of metastatic NSCLC patients would not be cost-effective due to the high cost of crizotinib and low prevalence of *EML4-ALK* mutation in a population of patients with NSCLC.

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TABLE OF CONTENTS

List of Tables

List of Figures

PART A: Targeted therapies in Non-Small Cell Lung Cancer (NSCLC)

INTRODUCTION

Lung cancer is the second most common type of cancer in both men and women. According to estimates from the American Cancer Society, about 221,200 new cases of lung cancer will be diagnosed in 2015.[18] Lung cancer accounts for about 13% of all new cancers in the United States.[18]

There are three main types of lung cancer: Non-Small Cell Lung Cancer (NSCLC), Small Cell Lung Cancer, and Lung Carcinoid Tumor. NSCLC is the most common type of lung cancer and accounts for about 85% of all lung cancers.[14] The subtypes of NSCLC include squamous cell carcinoma (SCC), adenocarcinoma, and large cell carcinoma.[14] Adenocarcinoma is the most common type of NSCLC followed by SCC.

Currently a majority of patients with NSCLC are treated with surgical resection and/or cytotoxic drugs. Patients with early stage non-metastatic cancer (stage IA-IB) usually undergo surgical resection.[14] Surgical resection along with chemotherapy is recommended for patients whose tumor has spread locally (stage IIA-IIIB).[14] Patients with advanced (stage IV) NSCLC are treated with chemotherapy.[1] Cytotoxic drugs such as cisplatin, carboplatin, docetaxel, paclitaxel, gemcitabine, and pemetrexed are used in chemotherapy. The above therapies have resulted in a modest increase in the overall survival of patients (median survival of 8 months with chemotherapy vs median survival of 5.7 months for patients without chemotherapy).[16] They have also been shown to result in a modest improvement in the patient's quality of life.

Advances have been made in understanding the molecular mechanisms of lung cancer. The discovery of new biomarkers, driver mutations and signaling pathways in NSCLC has changed the

treatment strategy for patients with NSCLC. The mutations which are responsible for both the initiation and maintenance of cancer are known as 'driver mutations'.[9] Genetic mutations thus play an important role in the development and progression of NSCLC. Specifically, mutations in *KRAS*, anaplastic lymphoma kinase (*ALK*), epidermal growth factor receptor (*EGFR*), fibroblast growth factor receptor (*FGFR*) genes, and other genes of the *PI3K/AKT* pathway are commonly observed in patients with NSCLC.[9],[14]

'Targeted therapies' or 'personalized medicine' in NSCLC include testing the tumor for driver mutations and tailoring the treatment against specific mutations found in the tumor.[12] Targeted therapies act on specific molecular targets that play an important role in growth or progression of a tumor. They do not interfere with rapidly dividing normal cells. Thus 'targeted therapies' have the potential to protect a patient from broad spectrum side effects associated with traditional therapies. Success in targeted therapies has been achieved for a small sub-set of NSCLC patients who harbor specific mutations.

EXAMPLES OF TARGETED THERAPIES IN NSCLC

Mutations in *EGFR* are observed in approximately 27% of the patients with adenocarcinoma. It was discovered that mutations in *EGFR* result in ligand independent activation of *EGFR* tyrosine kinase.[7],[14] Constant activation of *EGFR* tyrosine kinase promotes uncontrolled cell division. Following this discovery, *EGFR* tyrosine kinase inhibitors (*EGFR-TKIs*) such as gefitinib, erlotinib and afatinib were developed. They demonstrated improved efficacy as compared to traditional chemotherapy in patients with activating *EGFR* mutations.[7] Monoclonal antibodies (mABs) such as cetuximab and panitumumab have also demonstrated moderate clinical efficacy in the patients who harbor the similar mutations. These compounds block the *EGFR* receptor and mediate cytotoxicity of cancerous cells.[2]

The fusion of echinoderm microtubule associate protein like 4 (*EML4*) and anaplastic lymphoma kinase (*ALK*) genes has been identified as an oncogenic driver in NSCLC.[5] This fusion is found in approximately 5% of NSCLC patients and is commonly observed in non-smokers with adenocarcinoma. It is responsible for tumor progression, survival and cell proliferation in adenocarcinoma. Small molecule inhibitors like crizotinib have been shown to increase response rate and progression free survival in patients who harbor this mutation.[5] Resistance to crizotinib has also been observed in some patients. Small molecule inhibitors of *ALK* such as ceritinib and alectinib have been shown to overcome resistance to crizotinib.[14]

Molecular targets including the PI3K*AKT* pathway and fibroblast growth factor receptor *(FGFR)* have been identified in patients with squamous cell carcinoma (SCC). PI3K belongs to a family of lipid kinases which are responsible for cell proliferation, cell growth and cell differentiation. PI3K is regulated by a tumor suppressor gene called *PTEN*. Mutations that inactivate *PTEN* lead to hyper-activation of PI3K which leads to uncontrolled cell growth in SCC. Activation of PI3K is observed in around 33%-43% of SCC patients.[14]

PI3K inhibitors such as buparlisib (BKM120) and PX-866 are being evaluated in SCC. [14] Buparlisib has demonstrated anti-proliferative action against SCC with PI3K mutations in preclinical trials. Currently phase II trials with buparlisib have been initiated.[14],[20] PX-866 is similarly being evaluated in combination with docetaxel in an ongoing Phase II clinical trial. Preliminary data from the latter trial has demonstrated that PX-866 results in longer progression free survival in SCC patients with PI3K mutations.[8], [14], [21]

FGFR belongs to a family of tyrosine kinases. Deregulation of *FGFR* is responsible for tumor proliferation in SCCs. *FGFR* mutations are found in approximately 20% of SCC patient.[14] Tyrosine kinase inhibitors (TKIs) have been developed for treatment of SCC patients harboring

mutations in this gene. For example a combination therapy of nintedanib with platinum-based chemotherapy for SCC patients is currently in a Phase II clinical Trial.[14], [22]

MOLECULAR TARGETS UNDER INVESTIGATION

In addition to established targeted therapies, a number of emerging molecular targets are also under investigation. Mutations in *KRAS* and *TP53* are present in different types of malignancies such as pancreatic cancer, breast cancer, and lung cancer.[4] Thus mutations in *KRAS* and *TP53* are attractive as therapeutic targets. *KRAS* is a type of guanosine triphosphatase (GTPase) which is associated with many tumor signaling pathways like *MAPK* signaling pathway, PI3K/*AKT* signaling pathway.[4] Despite the prevalence of *KRAS* mutations in different types of cancers, direct targeting of *KRAS* mutations has been difficult.

KRAS mutations have been observed in around 8 % to 24 % of NSCLC cases.[1] These mutations are found in both adenocarcinomas and SCCs. Currently, many therapeutic agents targeting *KRAS* are under investigation. A GI-4000 *KRAS* vaccine, for example, is under investigation in patients with adenocarcinoma.[14]

TP53 acts as a tumor suppressor gene. It is found to be mutated in both adenocarcinomas and SCCs. Direct targeting of *TP53* in lung cancer has also been difficult due to the incomplete understanding of *TP53* mutation biology.[4] *TP53* is mutated across the entire coding sequence of the gene. This gives rise to everything from *TP53* deletions to gain of function mutations in lung cancer. Small molecules that inhibit the growth of cells with mutated *TP53* are being investigated. A clinical trial is currently evaluating the safety of a small molecule called APR-246 which theoretically can inhibit the growth of mutant *TP53* cells.[14],[23]

SURVIVAL BENEFITS FROM TARGETED THERAPIES

Several clinical trials have demonstrated improved progression free survival (PFS) and/or overall survival (OS) with targeted therapies for patients with NSCLC.

EGFR directed targeted treatments

The National Cancer Institute of Canada (NCIC) trial of erlotinib versus placebo demonstrated significant improvement in median survival (4.7 months to 6.7 months),higher response rates and longer survival in NSCLC patients with increased *EGFR* gene copy number.[4] The results demonstrated that certain NSCLC patients such as light smokers or never smokers, or NSCLC patients with adenocarcinoma, had increased *EGFR* gene copy number and thus were more likely to respond to therapy with and *EGFR* Tyrosine kinase inhibitor (*EGFR* TKI).[4]

The results of the Iressa Pan-Asia Study (IPASS) trial demonstrated that NSCLC patients known to have *EGFR* mutations had significant improvement in PFS (HR= 0.48, 95%: CI 0.36-0.64) from a first-line *EGFR* TKI like gefitinib.[4] Patients without *EGFR* mutations had shorter PFS after being treated with gefitinib.[4]

The European randomized trial of Tarceva versus Chemotherapy (EURTAC) randomized NSCLC patients with *EGFR* mutations from outside of Asia. The results demonstrated that patients treated with erlotinib had significant improvements in PFS compared to patients treated with a platinum doublet (HR =0.37, 95% CI: 0.25-0.54).[4]

Most of the trials described above also demonstrated that treatment-related mortality and severe toxicity (grade 3 or 4) from *EGFR* TKIs was less common than toxicities from cytotoxic chemotherapy. Thus discontinuation of therapy due to severe toxicities was also less common in patients receiving *EGFR* TKIs.[4]

EML4-ALK gene fusion targeted therapy

The results of two single-arm trials have demonstrated that crizotinib results in significant anti-tumor activity and overall survival NSCLC patients with *EML4-ALK* fusion rearrangements.

An open-label active-controlled multinational randomized trial called Profile 1007 trial, compared the anti-tumor activity of crizotinib with standard chemotherapy in *ALK*-positive NSCLC patients whose disease progressed after platinum-based doublet chemotherapy. The patients treated with crizotinib demonstrated superior progression-free survival (PFS) (HR=0.49, 95% CI: 0.37, 0.64) and overall response rate (ORR) (65% vs. 20%) compared to patients treated with standard chemotherapy. [17] However the trial also demonstrated elevated aminotransferase levels (grade 3 or 4) as a side effect in more than 5% of the patients treated with crizotinib.[17]Elevated aminotransferase did not cause any side effects in the patients.

Targeted therapies and emerging molecular targets in NSCLC are summarized in the following table (Table 1)

Table 1: Summary of Targeted Therapies in Lung Cancer.

Mutated Genes	**Proportion in Patients**	**Treatment**	**Survival Benefits**
EGFR	27% of patients with adenocarcinoma	Gefitinib, Erloitinib, Afatinib.	Higher response rates, improved PFS and longer survival.
EML4-ALK	5% of patients with NSCLC	Crizotinib	Improved PFS and overall response rate.
PI3K	33% to 43% of patients with SCC	Buparlisib,PX-866 (under evaluation)	Improved anti-proliferative action and improved PFS
FGFR	20% of patients with SCC	Combination therapy of Nintedanib with platinum based chemotherapy	Improved response rate.
KRAS	8% to 24 % of patients with NSCLC	GI-4000 KRAS vaccine (under investigation)	Theoretically increases immune response to mutant KRAS.
TP53	Variable in patients with SCC and adenocarcinoma.	APR-246 (under investigation)	Theoretically inhibits growth of TP53 mutant cells

DISCUSSION

Many targeted therapies such as *EGFR*-TKIs and crizotinib have demonstrated improved clinical efficacy in a subset of patients with specific mutations. These targeted therapies, which are often very expensive can be avoided in patients without the appropriate molecular mutations. Thus the targeted therapies have a potential to be cost-effective. Despite the successes of targeted therapies, there are many challenges that currently limit their adoption in clinical practice.

One of the most important challenges is that each of the above mentioned targeted therapies are successful in only a subgroup of patients, who typically represent only a small percentage of those with lung cancer. Thus, the majority of patients with lung cancer have to rely on traditional, non-targeted, approaches to chemotherapy. While less expensive, these non-targeted approaches are typically less effective and more often lead to treatment failures and/or complications from cytotoxicity, with additional cost implications.

Many different methods are available to test for molecular mutations in a tissue sample. Different methodologies require different expertise, different equipment and have different costs. For example *EGFR* mutations can be tested for by at least thirteen different methodologies. This can cause a variation in the sensitivity and validity of test results. So having standardized testing methods will be important to ensure reliability of test results.

Also tumor heterogeneity represents a major hurdle as the piece of the tumor used to identify relevant genetic mutations may not represent the entire tumor present in the patient's body. Different parts of the tumor may harbor different mutations. This may lead to development of resistance to the therapy.[11]

Some patients, perhaps the majority, will go on to develop drug resistance. This drug resistance can be primary, i.e patients are initially resistant to the treatment (despite tests suggesting the presence of driver mutations), or it can be acquired, i.e patients initially respond to treatment and subsequently develop resistance as susceptible cancer cell lineages are replaced by cells with different molecular drivers.[6] Several mechanisms, such as activating mutations, increased gene copy number, and the emergence of resistance conferring mutations, are thought to be responsible for developing drug resistance in patients.[23]

Researchers are working to understand the molecular basis of drug resistance to develop better therapies, including therapies that may target multiple driver classes simultaneously to forestall known patterns of drug resistance.

Finally, most of the targeted therapies for NSCLC and the companion molecular tests come at a very high cost to the patient and/or society. This raises important questions about the affordability and accessibility to novel targeted therapies.

CONCLUSION

Incorporation of genomics in the field of cancer holds great promise. Targeted therapies demonstrate a better safety profile and produce substantial improvements in survival for patients with specific mutations. But despite the advances in this field, there are several limitations that limit the adoption of targeted therapies in clinical practice. Targeted therapies should be clinically efficient and their toxicity must be manageable. It is also very important to accurately identify patients most likely to benefit from targeted therapies. Better targeted therapies are being developed as we deepen our understanding about the different mutations and biological pathways and their clinical relevance.

PART B: Cost-utility analysis

INTRODUCTION

In 2007, the fusion of echinoderm microtubule associate protein like 4 (*EML4*) and anaplastic lymphoma kinase (*ALK*) gene was identified as an oncogenic driver in NSCLC.[5] It is found in approximately 5% of NSCLC patients and is commonly observed in non-smokers with adenocarcinoma. The fusion gene results in a constitutive kinase activity and is responsible for tumor progression, survival and cell proliferation in adenocarcinoma.

Crizotinib is an oral small-molecule tyrosine kinase inhibitor. It inhibits the kinase activity of the fusion proteins.[17] In two single-arm trials, crizotinib has demonstrated significant anti-tumor activity in patients with *EML4-ALK* positive NSCLC patients.[17] Crizotinib was approved by the US Food and Drug Administration (US FDA) in November 2013 for treatment of patients with metastatic NSCLC that is *ALK* positive as detected by an FDA-approved test.[25],[26] The US FDA approved Vysis *ALK* Break Apart FISH Probe (Abbott Molecular) as a companion diagnostic test along with crizotinib. The Vysis *ALK* Break Apart FISH Probe test uses fluorescence in-situ hybridization (FISH) technique to detect rearrangements in the *EML4-ALK* fusion gene. The above test is the only available diagnostic assay that has been clinically validated to predict response to the targeted therapy with crizotinib.[5]

The FDA's approval was based on the results of an open-label active-controlled multinational randomized trial called Profile 1007 trial.[26] The trial compared the anti-tumor activity of crizotinib with standard chemotherapy in *ALK*-positive NSCLC patients whose disease progressed after platinum-based doublet chemotherapy. The patients treated with crizotinib demonstrated superior progression-free survival (PFS) and overall response rate (ORR) compared to patients treated with standard chemotherapy.

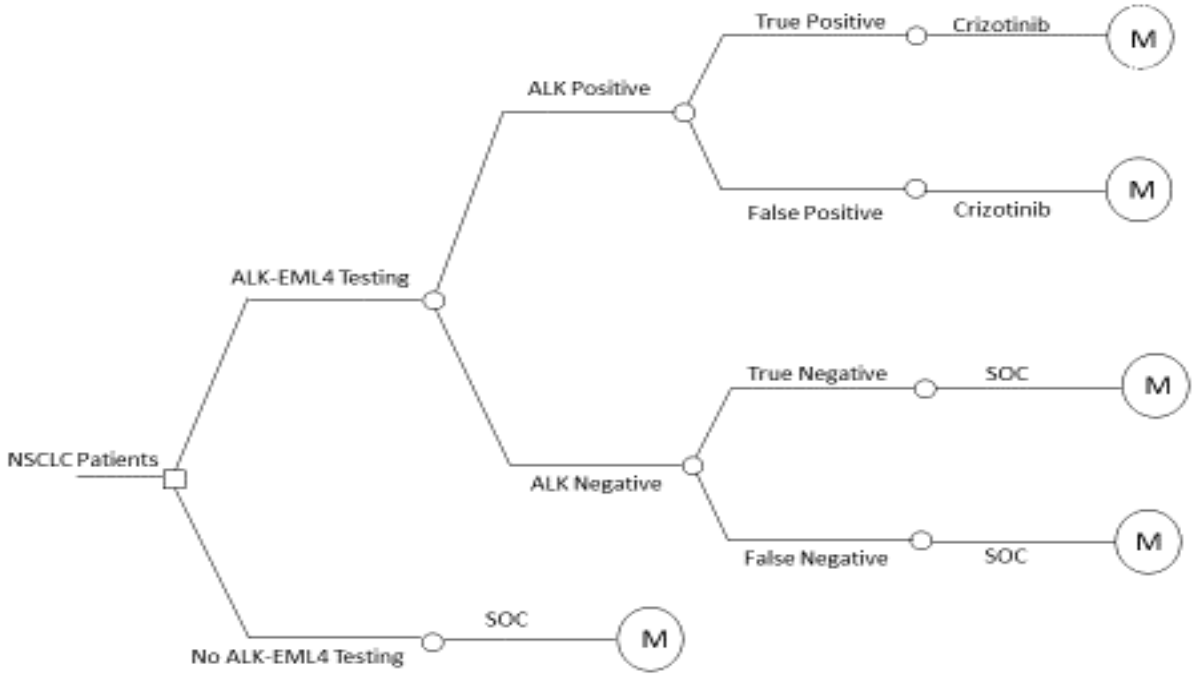
In this chapter, we have evaluated the cost-utility of *EML4-ALK* fusion testing with the FDA-approved Vysis *ALK* Break Apart FISH Probe (Abbott Molecular) in patients with advanced *EML4-ALK* positive NSCLC from a health-services payer perspective.

METHODS

Decision Tree and Drug Treatment.

A Markov model was developed with an upfront decision tree to categorize patients into treatment groups based on the *EML4-ALK* fusion testing or no testing options. A decision tree was developed to compare the lifetime benefits and direct costs associated with *EML4-ALK* fusion testing to no testing for one year in patients with metastatic NSCLC pretreated with platinum-based doublet chemotherapy. **(Figure 1).**

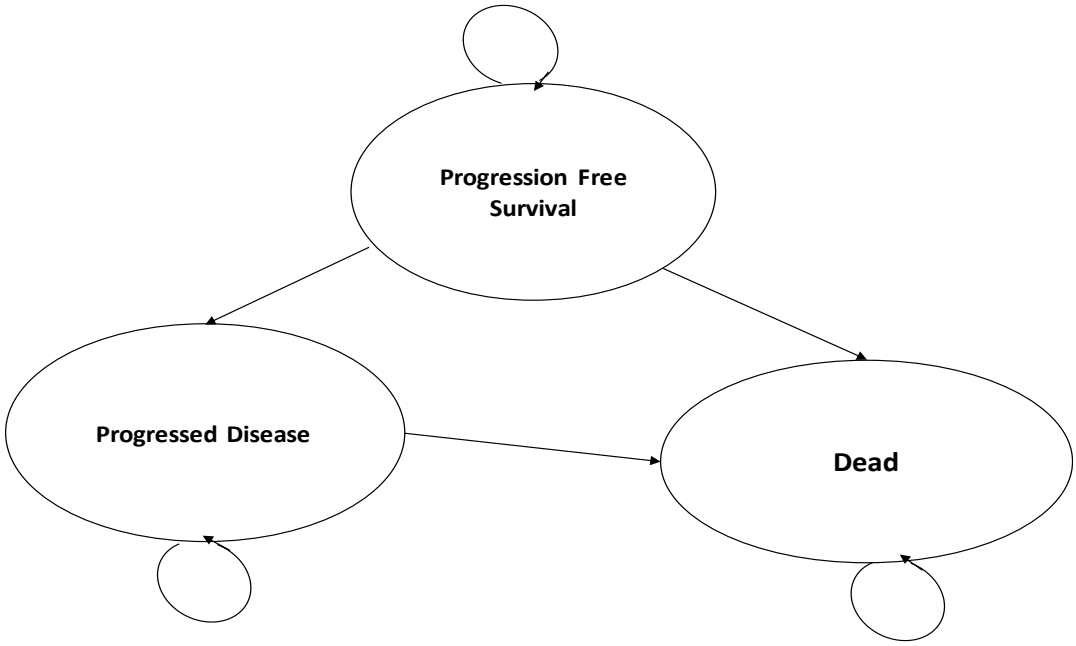
Figure 1: Decision Tree



A Markov model was developed to reflect disease progression with standard chemotherapy in NSCLC patients. **(Figure 2).** Patients could be in one of the following three states during the course of the treatment; Progression Free (PF) Disease, Progressed Disease (PD), or Death.

All patients start out in the PF state. From there they remain in the PF stage, transition to the PD stage or die. From the PD state, patients either remain in the PD state or die. Death is the absorbing stage, i.e. patients cannot transition to other stages after they die.

Figure 2: Markov Model



Patients who underwent *EML4-ALK* testing, either had *EML4-ALK* fusion rearrangements (*ALK* positive) or did not have *EML4-ALK* fusion rearrangements (*ALK* negative). Among the people who tested positive for *EML4-ALK* fusion rearrangements, some were 'True Positives' or 'TP' (Probability [*ALK* positive ǀ Test positive]) and some were 'False Positives' or 'FP' (Probability [*ALK* negative ǀ Test positive]).

All patients who tested positive for *ALK* rearrangements (*ALK* positive), were treated with crizotinib. The dosage of crizotinib is (250 mg twice daily) in a 3-week cycle.[6]Similarly, among the patients who tested negative for *ALK* rearrangements (*ALK* negative), some were 'True Negatives' or 'TN' (Probability [*ALK* Negative ǀ Test Negative]) and some were 'False Negatives' or 'FN' (Probability [*ALK* Positive ǀ Test Negative]).

Having tested negative for *ALK* rearrangements (*ALK* negative), all the patients were treated with standard of care (SOC). SOC was intravenous chemotherapy comprising either pemetrexed (500 mg per square meter of body-surface area) or docetaxel (75 mg per square meter)

once every 3 weeks.[17] Patients who did not undergo *EML4-ALK* testing, received SOC which is same as above. Both therapies were administered until treatment discontinuation due to adverse events or death.

Model Assumptions

The following assumptions were made in building the above model:

1) The patients who tested positive for *EML4-ALK* fusion rearrangements (*ALK* positive) were treated with only crizotinib.

2) The efficacy and effectiveness of the SOC did not depend on the status of *EML4-ALK* fusion rearrangements. Thus the treatment effect was same in case of *ALK* negative patients and in patients who did not undergo *EML4-ALK* testing.

3) The drug resistance that might have developed was not taken into account.

Economic Assumptions

Cost-utility analysis was performed from a health-services payer perspective. Direct medical costs included only the drug costs, the cost of the Vysis *ALK* Break Apart FISH Probe diagnostic test, and the medical costs associated with each state in the Markov model. Both the health benefits and the medical costs were discounted in order to convert them into their present-day value to account for the time value of money. The concept of 'time value of money' states that money is worth more today than in the future. A discount rate of 3% was used as it is the rate of return for the average consumer as per the federal Office of Management and Budget (OMB).[29] At this rate an average consumer is willing to substitute USD 100 today for a future consumption of USD 103 a year from today.[29]

Health benefits were expressed as Quality Adjusted Life Years (QALYs) gained. QALYs measure health benefits as a combination of the duration of life and quality of life .The incremental cost difference (ICD) was calculated as the difference in the expected costs of the two comparators. Similarly the incremental difference in the health benefits (IHD) was calculated as the difference in the expected QALYs produced by the two comparators. The incremental cost effectiveness ratio (ICER), also known as the cost per QALY was calculated by dividing ICD by IHD.

Probability Estimates

The prevalence of *ALK* rearrangements in patients with NSCLC is approximately 5%.[18] The sensitivity and specificity of the Vysis *ALK* Break Apart FISH Probe (Abbott Molecular) is 99%.The proportion of 'True Positives' and 'False Positives' was estimated using the following formulae:

1) (Probability [*ALK* positive ǀ Test positive])

= [(Sensitivity* Prevalence)/ [(Sensitivity*Prevalence) + (1-Specificity)*(1-Prevalance)]

2) (Probability [*ALK* Negative ǀ Test Negative])

= [Specificity*(1-Prevalance)]/ [(1-Sensitivity)*Prevalence) + (Specificity*(1-Prevalance)]

The annual transition probabilities for the Markov model were calculated using the data from the Profile 1007 trial.[5]

Probability of dying for patients with progression free disease [(PF⟶Dead)] in both the treatment groups was assumed to be similar to that of the general population. It was obtained from the general mortality tables.

Probability of surviving for patients with progression free disease in both the treatment groups was calculated from survival curves in Profile 1007 trial.[17]

Probability of dying for patients with progressed disease [P (PD⟶Dead)] in both the treatment groups was calculated by subtracting [P (PF⟶Dead)] from the total number of patients who died at the time of data cut-off in Profile 1007 trial.[17]

Utility Estimates

Utility estimates are used to measure the quality of life of individuals in a particular health state. Utilities are calculated by asking individuals to trade off improvements in their health state against either life expectancy (time trade-off) or risk of death (standard gamble).[30] Utility estimates are measured on a scale of 0 (a quality of life as bad as being dead) to 1 (a quality of life with best imaginable health).[30]

Utility estimates for different stages of NSCLC and different grade 3 or 4 toxicities commonly associated with chemotherapy treatments in our exercise, were obtained from a study in UK.[10] In this study, health states describing patients receiving second-line treatment for metastatic NSCLC were used.[10] The utility values for different health states used in this model are given in Table 2.

Table 2: Utility Values of Health States [10]

Health States	**Utility Values**
Stable Disease (without toxicity)	0.653
Progressive Disease	0.473
Responding Disease	0.673

A decrement of 0.014 was used for oral therapy (crizotinib) and a decrement of 0.043 was used for IV therapy (SOC).[10]

Average utility for crizotinib and standard of care to be used in the model was calculated by multiplying the proportion of people in different health states by the corresponding utility values. The data was used from the Profile 1007 trial.[17]

Utility decrements for side effects were not used in the above calculations because, the grade 3 or 4 side-effects in the Profile 1007 trial were minor.

Table 3: Adverse Events following treatment with Crizotinib and Standard Chemotherapy.[17]

Adverse Event	Crizotinib (N=172)		Chemotherapy (N=171)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	no. of patients (%)			
Vision disorder†‡	103 (60)	0	16 (9)	0
Diarrhea	103 (60)	0	33 (19)	1 (1)
Nausea§	94 (55)	2 (1)	64 (37)	1 (1)
Vomiting§	80 (47)	2 (1)	30 (18)	0
Constipation	73 (42)	4 (2)	39 (23)	0
Elevated aminotransferase levels†	66 (38)	27 (16)¶	25 (15)	4 (2)
Edema†	54 (31)	0	27 (16)	0
Fatigue	46 (27)	4 (2)	57 (33)	7 (4)
Upper respiratory infection†	44 (26)	0	22 (13)	1 (<1)
Dysgeusia	44 (26)	0	16 (9)	0
Dizziness†	37 (22)	1 (1)	14 (8)	0
Dyspnea†‖	23 (13)	7 (4)	32 (19)	5 (3)
Rash	15 (9)	0	29 (17)	0
Alopecia	14 (8)	0	35 (20)	0

Health Benefits (QALY) Estimates

Quality adjusted life-years (QALYs) measure health benefits as a combination of the duration of life and quality of life. Utility estimates are used to measure the quality of life and the proportion of people in each health state are used to measure the duration of life in that particular health state. The QALYs in our exercise were calculated by summing the average weighed utilities over a life-time horizon.

The patients either started in PF stage or the PD stage. The model was simulated for a duration of 10 years. At the end of 10 years, almost all the patients who had started either in the PF stage or the PD stage had died. The QALYs for both the testing options were then discounted at a rate of 3%.

Cost Estimates

Medicare reimbursement rates for 2013 were used to calculate the drug costs.[27],[28] The cost of crizotinib per person per month was USD 14,382, the cost of pemetrexed and docetaxel per person per month was USD 5,723 and USD 620 respectively.[27],[28] The proportion of people assigned to docetaxel and pemetrexed in the Profile 1007 trial was taken into account to calculate the total cost of SOC. The costs associated with states in the Markov model were calculated from a Medicare study done in 2000.[3],[13] The costs were converted to the currency value of 2013 using appropriate inflation rates. A discount rate of 3 % per year was applied to calculate the total cost over a lifetime horizon of 10 years.

Sensitivity Analysis

A one-way sensitivity analysis was performed to explore the robustness of our model's assumptions. The costs and the other parameters from the decision tree were varied by 25% to examine their effect on the ICER. A tornado diagram was constructed to show the results of the one way sensitivity analysis. A threshold analysis was also conducted to find the price of crizotinib at which the ICER equals a willingness to pay threshold (WTP) of USD 100,000.

RESULTS

The use of Vysis *ALK* Break Apart Probe test for *EML4-ALK* fusion testing in NSCLC patients pretreated with platinum-based doublet chemotherapy resulted in added health benefits of 0.4055 QALYs as well as additional cost of USD 56,938 for an average patient with NSCLC over a lifetime horizon. It results in the ICER of USD 140,414 per QALY gained.

Table 4: Probabilities, Utilities and Costs used for Analysis

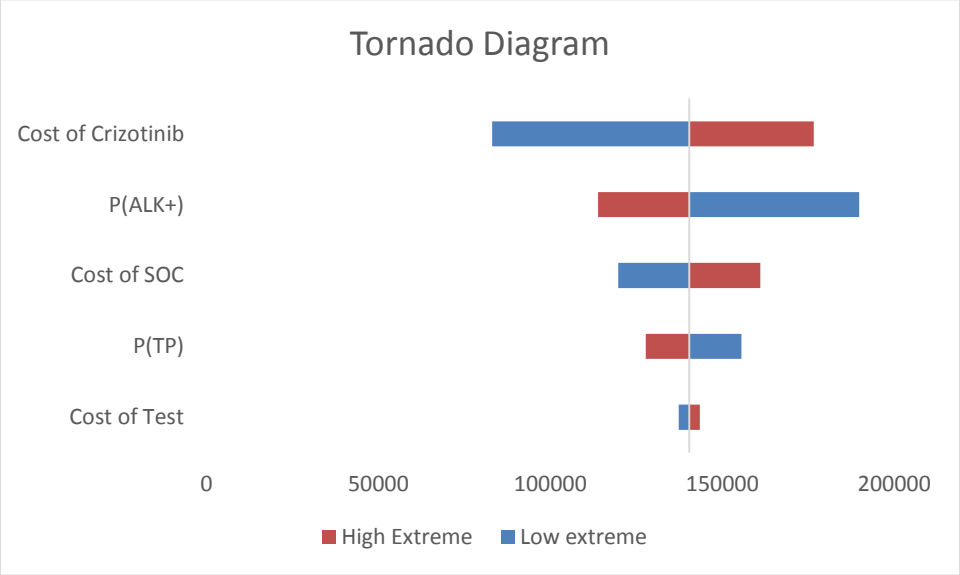
The yearly costs in the table are in 2013 USD.

Variable	Value
Probabilities	
ALK Positive	0.05
True Positive	0.8389
True Negative	0.9994
Utilities	
Crizotinib	0.584
Standard of Care	0.53
Progression Free (PF)	0.653
Progressed Disease (PD)	0.473
Costs	
Crizotinib	USD 172,590
Standard of Care	USD 76,140
Vysis ALK Break Apart FISH Probe	USD 574
T**ransition Probabilities**	
Standard of Care (SOC)	
PF ⟶ PD	0.764
PF ⟶ Dead	0.056
PD ⟶ Dead	0.104
Crizotinib	
PF ⟶ PD	0.594
PF ⟶ Dead	0.056
PD ⟶ Dead	0.094

Sensitivity Analysis

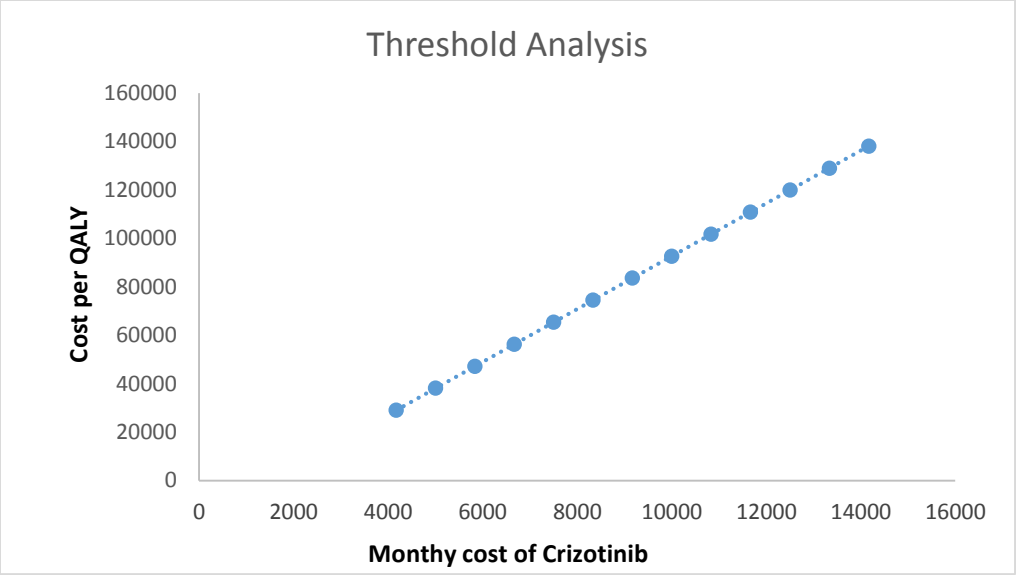
The results of the one-way sensitivity analysis were expressed in form of a tornado diagram. **(Figure 3)**

Figure 3: Tornado Diagram



The results indicate that the primary drivers of the ICER (cost per QALY) are the prevalence of *EML4-ALK* fusion mutations (P (ALK+)) in the population of patients with NSCLC and the cost of crizotinib. The ICER is less sensitive to higher frequency of *EML4-ALK* fusion genes in the population and much more sensitive to lower frequency of *EML4-ALK* fusion genes in the population. The ICER is less sensitive to high cost of crizotinib and more sensitive to low cost of crizotinib. The ICER is equally sensitive to high and low cost of standard of care. The ICER is not very sensitive to the cost of the Vysis *ALK* Break Apart FISH Probe test. On the basis of the results above, a higher frequency of *EML4-ALK* fusion genes in the population and lower cost of crizotinib would significantly reduce the cost per QALY.

Figure 4: Threshold Analysis Chart



Keeping all other variables constant, a reduction in the monthly price of crizotinib would significantly reduce the cost per QALY of testing for *EML4-ALK* status in NSCLC patients **(Figure 4)**. As per the Medicare reimbursement rates for 2013, the monthly cost of crizotinib was USD 14,382. A decrease of USD 3,000 in the monthly price of crizotinib would reduce the ICER by almost USD 40,000. Thus a reduction in the price of crizotinib alone would decrease the ICER to a willingness to pay threshold of USD100,000 per QALY.

DISCUSSION

A Markov model was developed with an upfront decision tree to categorize patients into treatment groups based on the *EML4-ALK* fusion testing or no testing options. We calculated the ICER for the two comparators. The results indicate that *EML4-ALK* fusion testing with Vysis *ALK* Break Apart FISH probe test followed by targeted treatment with crizotinib in patients with NSCLC is not cost effective at the current willingness to pay (WTP) threshold.

The WTP thresholds used for comparison have been established in the United States based on a retrospective analysis of existing practice. The threshold of USD 50,000 per QALY gained is commonly used in cost-effective analyses. This threshold was based on the cost-effective analysis of dialysis of chronic renal disease.[19] It has been updated to USD 100,000 per QALY gained.[19] Testing for *EML4-ALK* mutations with the Vysis *ALK* Break Apart FISH probe test followed by targeted crizotinib treatment resulted in health gain of 0.4055 quality adjusted life years (QALYs) and an increased cost of USD 56,938 over a life-time horizon. It resulted in the ICER of USD 140,414 per QALY gained over a life-time horizon.

Vysis Break Apart FISH probe test is used to aid in identification of NSCLC patients eligible for treatment with crizotinib. It is the only available diagnostic assay that has been clinically validated to predict response to the targeted therapy with crizotinib. The results of the sensitivity analyses demonstrated a large impact of the cost of crizotinib and the low prevalence of *EML4-ALK* mutations on the cost-effectiveness of testing for *EML4-ALK* mutations with Vysis Break Apart FISH probe test in NSCLC patients. Therefore, very significant cost reductions in the price of crizotinib would be needed to make testing for *EML4-ALK* mutations with Vysis *ALK* Break Apart FISH probe test cost- effective at the current frequency of *EML4-ALK* fusion rearrangement (5%).

According to the American Cancer Society, about 221,200 new cases of lung cancer were diagnosed in 2015.[18] Out of 221,200 cases of lung cancer, approximately 188,020 patients (85%) would have NSCLC. Out of 188,020 patients, approximately 9401 (5%) patients would harbor the *EML4-ALK* fusion rearrangements and thus would be eligible for treatment with crizotinib. The annual cost of testing for *EML4-ALK* mutations and treatment with crizotinib is USD 172,590 as per the dollar estimates of 2013. Therefore the yearly cost of treating approximately 9,401 patients with crizotinib would be more than a billion USD.

Testing for specific mutations can help to identify a subset of patients who can benefit from targeted therapies. Targeted therapies can also prevent costs due to ineffective treatments and unnecessary toxicities. Genomic technologies thus help to use targeted therapies in select populations. But a small frequency of the target population may drive up the costs of targeted or personalized medicines. However, with panel testing, i.e. testing for multiple markers with one test, the value of testing is likely to improve

This study has several limitations. Our results cannot be generalized due to the following assumptions made in building the model;

1) The patients who tested positive for *EML4-ALK* rearrangements were treated with only crizotinib.
2) The efficacy and effectiveness of the standard of care (SOC) did not depend on the status of *ALK* rearrangements. Thus the treatment effect was same in case of *ALK* negative patients and in patients who did not undergo *EML4-ALK* testing.
3) All the patients responded to the drug treatments.

In addition, we have only calculated the cost of the drugs, the cost of the Vysis *ALK* Break Apart FISH probe test and the medical costs associated with each state of the Markov model. We have not taken into account any resistance to treatment that might develop and the cost associated with it. We have only performed a one-way sensitivity analysis, in the form of a tornado diagram, to identify variables with a significant effect on the ICER. In addition to deterministic sensitivity analysis, a probabilistic sensitivity analysis where the input values of all major parameters can be varied would give a better understanding about the uncertainties in the model. We have used the utility values calculated from the perspective of NSCLC patients. Utility values calculated from a societal perspective might yield different results.

In conclusion, the results of our study indicate that testing for *EML4-ALK* mutations with Vysis *ALK* Break Apart FISH probe test followed by treatment with crizotinib in a population of NSCLC patients is not cost-effective at the WTP threshold currently adopted in the USA. A lower cost of crizotinib and an increase in the number of patients eligible for testing would help to make the above strategy more cost-effective.

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