Supplementary Material for "Budget Impact Analysis of Comprehensive Genomic Profiling in Patients with Advanced Non-Small Cell Lung Cancer"

# Introduction

This appendix supplements the methodological descriptions in the manuscript. This section provides additional detail on assumptions and calculations used in the budget impact analysis.

# Target Population

The number of patients covered by a hypothetical US health plan was assumed to be 2 million. The age and sex distribution of covered patients was assumed to match the US population. The annual incidence of NSCLC was calculated based on age-specific incidence rates and stratified by sex. Incidence rates in men and women (per 100,000) were 14.6 and 12.3 for age < 65 years, respectively; and 305.0 and 207.8 for ages ≥ 65 years, respectively. The proportion with advanced stage NSCLC at diagnosis was 79%. These epidemiological statistics were drawn from the Surveillance, Epidemiology, and End Results (SEER) Medicare database [1].

The number of incident cases of NSCLC was calculated by multiplying the total number of covered patients (2 million) by the NSCLC annual incidence rate per person. This implied a total of 674 covered patients developing NSCLC. This number was then multiplied by 79% to arrive at the population of covered patients diagnosed with advanced NSCLC (ie, eligible for molecular testing). Based on analyses of the OptumHealth Care Solutions database, approximately 50% of patients with advanced stage NSCLC receive molecular testing, resulting in a final cohort of 266 covered patients receiving molecular testing. Among 266 patients in the base case, 5 patients underwent CGP and the remainder 261 underwent non-CGP molecular diagnostic testing.

# Molecular Diagnostic Testing

Our model considered two types of molecular diagnostic testing: comprehensive genomic profiling (CGP), represented by FoundationOne, and non-GGP testing, represented as a mix of conventional and NGS-based tests for single genes and small NSCLC panels.

The alterations considered in this model included *EGFR*, *ALK*, *ROS1*, *HER2*, *BRAF*, *MET*, *RET* and *KRAS*; other loci that can inform clinical trial enrolment, including those with targeted therapies available through clinical trials, were studied as an aggregated group. For each alteration, the percentage of alterations detected was assumed to differ for FoundationOne or NGS compared to conventional molecular diagnostic testing, with greater sensitivity for FoundationOne/NGS. While one published study has shown that FoundationOne identified alterations in 26% of those patients who tested negative on conventional testing [2], the results of this study were not used in the present analysis. Rather, more conservative sensitivities of detection were drawn from large population studies reporting detection rates by locus [3]. Since mutation frequencies differ by histology, the distribution between non-squamous and squamous histology was set at 70% and 30%, respectively and used to calculate a weighted average for the prevalence of alterations. The testing rate for the conventional testing group was calculated based on a mix of potential tests for genomic alterations. Sixty percent were assumed to be panel tests for specific alterations within common genes, among these 10% were assumed to be NGS and 50% were non-NGS, 20% were assumed to be tests for *EGFR* only, and 20% were assumed to be tests for *ALK* only. Thus, 80% are tested for EGFR, 80% are tested for ALK and 60% are tested for alterations at the remaining loci listed above.Unfortunately, there is no clinically meaningful actionable mutation for squamous cell histology. The prevalence of other loci that could inform clinical trial enrollment, as a group, in non-squamous cancer was calculated based on Suh et al [4] which reported the collective prevalence of such alterations for the following loci: *STK11*, *MYC*, *RICTOR*, *CDK4*, *CCND1*, *BRCA2*, *BRCA1*, *NTRK1*, and *NTRK3*. The pan-negative cohort for conventional loci represented 19.6% of all cases, of which approximately 52% had mutations at the loci listed above. The overall prevalence of alterations at these loci was calculated as the proportion in the pan-negative cohort multiplied by the proportion in the pan-negative cohort with mutations: 19.5% × 52% = 10%. The prevalence of other alterations in NSCLC with squamous cell histology was calculated based on the prevalence of reported *PIK3CA* (20%) and *FGFR* (20%) alterations [5]. A summary of the detection rates among patients tested for the specific loci and the detection rates in the population that receives any molecular testing for FoundationOne and non-CGP molecular diagnostic testing is presented in Table S1.

Sensitivity analyses were conducted to assess changes in testing rates by non-NGS and NGS. In this scenario, *EGFR* and *ALK* were testing at 55% in non-NGS and 20% in NGS while the remaining alterations were tested at 30% non-NGS and 20% NGS. The total alterations were calculated as the product of alterations detected among those tested in the convention and non-NGS testing rate, added to the product of alterations detected among those tested in the FoundationOne and NGS testing rate. The values used in the sensitivity analyses are shown in parenthesis in Table S1 and results are shown in Figures 3 and 4 of the manuscript.

Based on molecular diagnostic testing and alterations detected, patients received either targeted therapy (listed in NCCN Guidelines® or available through clinical trials) or not targeted therapy. The proportion of patients for whom targeted therapy was available based on expected test results was calculated as the sum of total variants detected for loci with targeted therapies in Table S1. The remainder were deemed to have no targeted therapy available. Because treatment is not always assigned based on actionable alterations, we allowed for a distribution across all treatment types to be impacted by alteration status. The proportions of patients assigned to each treatment type, conditional on mutation status, are shown in Table 2 of the manuscript.

Given a treatment type, patients were then assumed to receive a specific form of treatment. All estimates were derived from expert opinion regarding the expected proportion of patients receiving a specific type of treatment given a specific alteration status, independently of the molecular testing modality that was used. These estimates are presented in Table S2.

The fraction and number of patients with advanced NSCLC assigned to different treatment types was calculated by multiplying the proportion of patients assigned to each of the three treatment groups (Manuscript - Table 2) by the proportion receiving each specific type of treatment. For example, in the CGP arm, of the 31.1% of patients assigned to the "available targeted therapies listed in NCCN Guidelines®" group, 64% received matched targeted therapy (representing 31.1% x 64% = 19.9%) and of the 41.4% assigned to the "not listed in NCCN Guidelines®" group 5% received matched targeted therapy (representing 41.4% x 5% = 2.1%), resulting in a total of 19.9% + 2.1% = 22.0% receiving matched targeted therapy. The distribution of patients receiving different types of treatment tabulated in the lower portion of Table 2 in the manuscript was calculated in a similar fashion, drawing from the upper portion of Table 2 and from Table S2. The resulting distribution was validated against clinical expert input and recent publications of treatment distributions as described in the manuscript.

# Overall Survival

Overall survival (OS) rates by treatment type and line of therapy were based on findings by Barlesi et al [8]. Findings suggest that patients with an actionable mutation had median OS of 16.5 months for first-line therapy compared with 11.8 months among those without an actionable mutation. The efficacy reported in Barlesi et al [6]was adjusted to reflect that one-third of patients with actionable mutations receive treatment under the assumption that treatment efficacy was the same for patients both with and without mutations. Therefore, the equation used to estimate OS for first-line, matched targeted therapy was calculated as OS × 1/3 + 11.8 × 2/3 = 16.5 months. This equation yields a matched targeted therapy OS estimate of 26 months.

Second-line OS was calculated as the difference between first-line OS and first-line progression-free survival (PFS) for matched targeted therapy and chemotherapy. Third-line OS was calculated similarly as the difference between second-line OS and second-line PFS for matched targeted therapy, chemotherapy, and immunotherapy. Matched clinical trial OS was assumed to be the average of OS in matched targeted therapy and chemotherapy across all lines of treatment, reflecting the fact that patients may be randomized to different treatment options in trials, and that not all investigational agents are effective. Non-matched targeted therapy and non-matched clinical trial OS were assumed to be the same as chemotherapy in all lines of treatment. OS associated with chemotherapy was assumed to be the same as the OS among those without an alteration (11.8 months).

Total OS by treatment type was calculated as the weighted average of OS across lines of therapy (Table S3). OS for the FoundationOne and conventional molecular tests were calculated by multiplying the weighted average survival for each treatment type by the number of patients receiving that treatment type. Estimated OS was 211.3 years for FoundationOne and 188.0 years for conventional molecular testing. These calculated average survival durations were validated against clinical expert input.

# Costs

The total cost of care per patient was calculated as the sum of anticancer drug and administration costs, diagnostic test costs, biopsy costs, and all medical services incurred by patients with metastatic NSCLC, divided by the number of patients in the category.

## Monthly Costs of Anticancer Drug Therapy

The representative treatments for each treatment type were as follows:

* Matched targeted therapy: erlotinib, afatinib, crizotinib and ceritinib
* Non-matched targeted therapy: bevacizumab and ramucirumab
* Immunotherapy: nivolumab
* Chemotherapy: pemetrexed

As the index therapy, matched targeted therapy costs were assumed to be an average of the monthly costs of erlotinib, afatinib, crizotinib and ceritinib. Non-matched therapy costs were assumed to be the average monthly costs of bevacizumab and ramucirumab. Chemotherapy costs were assumed to be the monthly cost of pemetrexed and monthly administration costs. Immunotherapy costs were assumed to be the monthly cost of nivolumab. As described in the manuscript text, the monthly costs for drugs in clinical trials were assumed to be 25% of the monthly cost of chemotherapy, assuming that half of the patients in trials enter randomized trials and half of those receive chemotherapy, for which costs are incurred, with all other patients receiving investigational drugs for which costs are not incurred by payers.

The monthly cost of subsequent treatment was calculated as a weighted average of the costs and assumed distribution of subsequent therapies given the index therapy (Table S4).

## Drug Therapy Duration

Patients receiving any diagnostic testing, and eligible for CGP, were assumed to be distributed across lines of therapy with 30% as first-line therapy, 50% as second-line therapy, and 20% as third- or later-line therapy based on expert opinion. The treatment duration of the index therapy was based on PFS and assumed using estimates from Barlesi et al [6] as described in Table S5. The Barlesi et al [6] results suggest that patients with an actionable mutation had median PFS of 10.0 months (first-line) compared with 7.1 months among those without an actionable mutation, and 3.4 versus 3 months, respectively, in second-line therapy. As explained in the discussion of OS by treatment type, approximately one-third of patients with a mutation received matched therapy. Similarly, the efficacy reported in Barlesi et al [6] was adjusted under the assumption that treatment efficacy was the same for patients both with and without mutations. Therefore, the equation PFS × 1/3 + 7.1 × 2/3 = 10.0 months was used to estimate PFS associated with matched targeted therapy, yielding a matched targeted therapy PFS estimate of 16 months.

The treatment durations of matched targeted therapy, immunotherapy and chemotherapy in the first and second lines were based on the PFS of the representative treatments reported in clinical trial publications. Third- or later-line treatment duration was assumed to be half of the second-line treatment duration for most treatments, except for immunotherapy. Patients tended to stay on immunotherapy after disease progression, thus the duration on third- or later-line treatment was assumed to be longer. The treatment durations of non-matched targeted therapy and non-matched clinical trials were assumed to be the same as chemotherapy and duration of matched clinical trials were assumed to be the average of matched targeted therapy and chemotherapy.

The treatment durations of subsequent therapies were calculated as OS minus treatment duration of the index treatment.

## Total Anticancer Drug Costs

Anticancer drug cost per patient by treatment type was calculated as the sum of total costs for the index therapy and total costs for subsequent therapy, all divided by the number of patients in the treatment type. The total costs for the index therapy were calculated as the monthly cost of treatment multiplied by the average duration of the index treatment for each treatment type weighted by the distribution of line of therapy. The total cost for subsequent therapy was calculated similarly using the average duration of the subsequent treatment for each treatment type.

## Medical and Testing Costs

The per-test cost of non-CGP was calculated based on a mix of conventional and NGS-based tests for small panels and single genes described above. Costs were based on data for panel tests for all known NSCLC genetic mutations (CPT code: 81445), tests for *EGFR* only (CPT code: 81235), and tests for *ALK* only (CPT code: 88374). The cost of a single non-CGP test was estimated to be $346. Based on analysis of the OptumHealth Care Solutions database, the rate of repeated testing per month for a convention test was 0.12 times per month. The cost of testing via FoundationOne was assumed to be $5800. Total diagnostic costs per patient by treatment type were calculated as the product of the cost of a single test times the expected number of required tests over the patient's lifetime as a function of the rate of repeated testing per month and OS by treatment.

Biopsy costs for non-NGS testing included costss incurred during the first biopsy and subsequent biopsies throughout the survival period. The cost of a single biopsy was estimated to be $226 for both CGP and non-CGP tests. The rate of repeated testing per month was estimated to be 0.10 for non-CGP testing based on analysis of the OptumHealth Care Solutions, Inc. database. The analysis assumes only 1 biopsy is necessary for CGP (using the FoundationOne test). Similar to the calculation of total diagnostic costs, total biopsy costs per patient by treatment type were calculated as the product of cost of a biopsy and the expected number of required biopsies over the patient's lifetime as a function of the rate of repeated testing per month and OS by treatment.

Monthly medical service costs were estimated to be $6,986.61 based on analysis of the OptumHealth Care Solutions, Inc. database. Total medical costs were calculated as the product of monthly medical costs and the length of OS by treatment type and line of therapy.

## Calculations of Aggregate Impacts on Costs and Life Years

Total life years and costs were calculated as the weighted average of OS and overall costs for CGP and non-CGP testing weighted by the proportion of the eligible population receiving CGP. With a base case of 2% receiving CGP and an increased scenario to 10%, total life years equalled 190.1 years and 191.8 years, respectively, for a difference of 1.7 life years after the increase. The increase in total costs was $1513 per patient with any molecular testing from a base case scenario cost of $107,262.

The budget impact per member per month (PMPM) of increasing the proportion of eligible patients receiving CGP from 2% to 10% is calculated as the total increased cost for the eligible population ($1513 × 266) divided by the total covered population per month. This equates to $0.02 PMPM.

The number of patients needed to test with CGP versus non-CGP testing to add 1 life year was calculated as the eligible patient population divided by the gain in life years from testing with CGP vs. non-CGP (266 patients / [211.4−189.7]), resulting in 12.3 patients.

# Tables

Table S1. Genomic Alterations and Detection Assumptions

|  |  |  |
| --- | --- | --- |
| Alterations | CGP (FoundationOne), % | Non-CGP, % |
| Testing rate | Alterations detected (among tested) [4, 5] | Total alterations detected in all patients | Testing rate in %(non-NGS/NGS)\* | Alterations detected(among tested) [5, 7, 8, 9] | Total alterations detected in all patients |
| Alterations with targeted therapies listed in NCCN Guidelines® |
| *EGFR* | 100 | 14.0 | 14.0 | 80(70/5 - 55/20)  | 12.1 (11.9) | 9.7 (9.0-9.3) |
| *ALK* | 100 | 2.9 | 2.9 | 80(70/5 - 55/20)  | 2.2 (2.1) | 1.8 (1.6-1.7) |
| *ROS1* | 100 | 1.0 | 1.0 | 60(45/5 - 30/20) | 0.8 (0.7) | 0.5 (0.4) |
| *HER2* | 100 | 4.2 | 4.2 | 60(45/5 - 30/20)  | 2.5 (2.1) | 1.5 (1.2-1.5) |
| *BRAF (V600E)* | 100 | 1.5 (4.0) | 1.5 (4.0) | 60(45/5 - 30/20)  | 1.4 (1.4) | 0.8(0.8-1.2) |
| *MET* | 100 | 5.8 | 5.8 | 60(45/5 - 30/20)  | 3.1 (2.6) | 1.9 (1.5-1.9) |
| *RET* | 100 | 1.7 | 1.7 | 60(45/5 - 30/20)  | 0.9 (0.7) | 0.5 (0.4-0.6) |
| Alterations with targeted therapies not listed in NCCN Guidelines® |
| *KRAS* | 100 | 22.4 | 22.4 | 60(45/5 - 30/20)  | 17.5 | 11.0 (9.0-9.7) |
| Other alterations with targeted therapies | 100 | 19.0 | 19.0 | 0 | 0 | 0 |

NCCN Guidelines®, National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology.

\* non-NGS testing rates and NGS testing rates used in sensitivity analysis are shown in parenthesis

Table S2. Proportion of Patients Receiving Each Treatment Type (Rows), Conditional on Alteration Status (Columns), Based on Clinical Expert Input

|  |  |  |
| --- | --- | --- |
| Type of treatment received | Informative alterations detected, % | No informative alterations detected, % |
| Treatment listed in NCCN Guidelines® | Not listed in NCCN Guidelines® |
| Targeted therapy | 64.0 | 5.0 | 10.0 |
| Immunotherapy | 10.0 | 30.0 | 30.0 |
| Chemotherapy | 10.0 | 30.0 | 30.0 |
| Clinical Trial | 6.0 | 10.0 | 5.0 |
| No drug treatment | 10.0 | 25.0 | 25.0 |
| Total | 100.0 | 100.0 | 100.0 |

NCCN Guidelines®, National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology.

Table S3. Overall Survival by Line of Therapy

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | First-line, months | Second-line, months | Third-line and above, months | Weighted average by line, months |
| Matched |  |  |  |  |
| Targeted therapy | 26 | 10 | 6 | 14 |
| Clinical trial | 19 | 8 | 4 | 11 |
| Non-matched |  |  |  |  |
| Targeted therapy | 12 | 5 | 2 | 7 |
| Immunotherapy | 19 | 12 | 9 | 14 |
| Chemotherapy | 12 | 5 | 2 | 7 |
| Clinical trial | 12 | 5 | 2 | 7 |
| No drug treatment | 5 | 3 | 2 | 3 |

Table S4. Distribution of Subsequent Therapies by Index Treatment

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Subsequent line of therapy distribution | Matched therapy, % | Clinical trial of matched therapy, % | Non-matched targeted therapy, % | Immunotherapy, % | Chemotherapy, % | No drug treatment, % |
| Matched therapy | 30 | 20 | 0 | 0 | 30 | 20 |
| Clinical trial of matched therapy | 0 | 0 | 0 | 0 | 50 | 50 |
| Non-matched targeted therapy | 0 | 0 | 0 | 0 | 70 | 30 |
| Immunotherapy | 0 | 0 | 0 | 0 | 50 | 50 |
| Chemotherapy | 0 | 0 | 0 | 30 | 30 | 40 |

Table S5. Assumptions for Treatment Duration of Index Therapy

|  |  |  |  |
| --- | --- | --- | --- |
| Treatment type | Line 1, months | Line 2, months | Line 3, months |
| Matched |  |  |  |
| Targeted therapy  | 16.0 | 4.0 | 2.0 |
| Clinical trial | 11.5 | 3.5 | 2.0 |
| Non-matched |  |  |  |
| Targeted therapy | 7.0 | 3.0 | 2.0 |
| Immunotherapy  | 12.0 | 4.0 | 3.0 |
| Chemotherapy | 7.0 | 3.0 | 2.0 |
| Clinical trial | 7.0 | 3.0 | 2.0 |

# References

1. National Cancer Institute. Cancer stat facts: Lung and bronchus cancer 2017 [cited 2017 April 20]. Available from: <https://seer.cancer.gov/statfacts/html/lungb.html>

2. Drilon A, Wang L, Arcila ME, et al. Broad, hybrid capture-based next-generation sequencing identifies actionable genomic alterations in lung adenocarcinomas otherwise negative for such alterations by other genomic testing approaches. Clin Cancer Res 2015;21:3631-9

3. Presley CJ, Soulos PR, Chiang AC, et al. Disparities in next generation sequencing in a population-based community cohort of patients with advanced non-small cell lung cancer. American Society of Clinical Oncology; 2017.

4. Suh JH, Johnson A, Albacker L, et al. Comprehensive genomic profiling facilitates implementation of the National Comprehensive Cancer Network Guidelines for lung cancer biomarker testing and identifies patients who may benefit from enrollment in mechanism-driven clinical trials. Oncologist 2016;21:684-91

5. Heist RS, Sequist LV, Engelman JA. Genetic changes in squamous cell lung cancer: a review. J Thorac Oncol 2012;7:924-33

6. Barlesi F, Mazieres J, Merlio JP, et al. Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT). Lancet 2016;387:1415-26

7. Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol 2012;30:863-70

8. Gainor JF, Shaw AT. Novel targets in non-small cell lung cancer: ROS1 and RET fusions. Oncologist 2013;18:865-75

9. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA 2014;311:1998-2006