# Cost Impact of Next Generation Sequencing Testing in NSCLC With and Without RNA Sequencing

EE321

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## Background

- In oncology, next generation sequencing (NGS) tests are used to identify biomarkers to inform the selection of targeted therapy as directed by clinical guidelines and/or regulatory approvals, and to inform clinical trial eligibility.[1]
- Due to the large number of potential oncogenic drivers in advanced non-small cell lung cancer (NSCLC), NGS is guideline-recommended for identifying actionable targets to inform treatment decisions.[2]
- Recent publications discuss the value of RNA sequencing in detecting fusions that may not be detected by DNA sequencing alone, including within NSCLC.[3,4]
- Current genomic tests include those based on DNA sequencing and those based on both DNA + RNA sequencing.[5] In cases where an initial test based on DNA sequencing is negative, clinicians may order a reflex RNA test.[6]
- Choice of an initial test can therefore impact diagnostic costs, as DNA sequencing alone could lead to underutilization of targeted therapies due to missing actionable fusions, whereas use of reflex testing incurs an additional charge and could delay the initiation of therapy.[6]

## Objective

Given the potential for improved detection of actionable fusions using RNA sequencing, we examined the costs for NSCLC patients receiving NGS tests that include DNA + RNA sequencing compared to costs of testing based strictly on DNA sequencing, with or without reflex RNA testing.

## Methods

- A Microsoft Excel-based model was developed to assess advanced/metastatic NSCLC patients.
- Three hypothetical screening approaches were compared:
    1. NGS testing with DNA-only sequencing
    2. NGS testing with DNA-only sequencing initially, followed by reflex RNA testing in those without a detected alteration
    3. NGS testing with DNA + RNA sequencing upfront
- DNA-only and DNA + RNA tests only differed in their ability to detect RNA fusions; all other aspects were equivalent.
- A range of 2.5-14% was considered for the prevalence of fusions detected by RNA but not DNA sequencing based on a range of estimates found in the literature.[7,8]
- DNA + RNA testing was assumed to detect all alterations. Test sensitivity was reduced in DNA-only sequencing to account for fusions missed with RNA sequencing. False positives were not incorporated into the model.
- Treatment pathways based on NGS test result were defined based on National Comprehensive Cancer Network guidelines[2] and expert opinion.
- Epidemiologic and economic inputs were based on published literature (**Table 1**).
- Test costs were based on generic CPT codes for large panel NGS tests.[9]
- Pharmacy costs were treatment-specific based on wholesale acquisition prices.[10]
- Productivity costs were included and differed based on whether treatment regimens included chemotherapy.[11]
- Model outcomes included the proportion of patients with actionable alterations detected by testing modality, as well as annual costs inclusive of all direct medical costs and productivity losses (2022 US dollars).

### Table 1. Model Inputs

| Model Input | Value | Reference(s) |
|---|---|---|
| Prevalence of alterations for which there are FDA approved therapies | 67.2% | 12-14 |
| Prevalence of alterations for which there are ongoing clinical trials | 25.6% | |
| Test costs | $2,919 | 9: CPT code 81455 |
| Biopsy costs | $304 | 15 |
| Reflex RNA costs | $3,675 | 9: CPT code 0019U |
| Average annual pharmacy costs | | |
| Targeted therapy | $146,336 | 10,16 |
| Standard of care | $108,696 | |
| Average annual other direct medical costs | | |
| Targeted therapy | $126,896 | 16,17 |
| Standard of care | $126,127 | |
| Average annual productivity losses | | |
| Targeted therapy | $645 | 11,18 |
| Standard of care | $2,139 | |

## Results

- The proportion of patients with actionable alterations when using DNA sequencing without RNA sequencing or without a reflex RNA test ranged from 79.8% - 90.5%, depending on the prevalence of RNA fusions (**Table 2**).
- RNA fusion prevalence did not impact the proportion of alterations detected when utilizing screening approaches that incorporated RNA sequencing, including use of an initial DNA + RNA test and the strategy of utilizing a reflex RNA test.

### Table 2. Proportion of Patients with Actionable Alterations* Detected by Testing Method

| % of Patients with RNA Fusions | DNA + RNA | DNA-only | DNA-only + Reflex RNA | Difference (DNA + RNA minus DNA-only) |
|---|---|---|---|---|
| 2.5% | 92.8% | 90.5% | 92.8% | 2.3% |
| 5% | 92.8% | 88.2% | 92.8% | 4.6% |
| 10% | 92.8% | 83.5% | 92.8% | 9.3% |
| 14% | 92.8% | 79.8% | 92.8% | 13.0% |

*Actionable alteration defined as an alteration for which there is an FDA approved treatment or an ongoing clinical trial. Differences between columns due to fusions missed without RNA sequencing. Model assumed only one actionable alteration per patient.

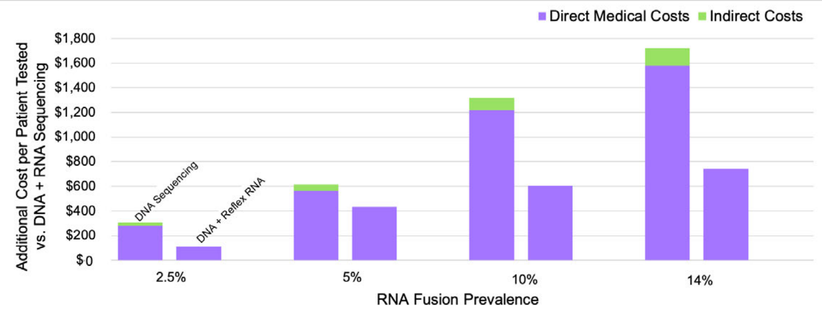
- Upfront DNA + RNA sequencing is cheaper per NSCLC patient compared with reflex RNA testing. Cost difference ranged from $400 when assuming the prevalence of RNA fusions was 2.5% to $741 with 14% additive detection (**Table 3**).
- DNA + RNA sequencing costs are not impacted by fusion prevalence and is the least expensive approach.
- Use of reflex RNA testing increases costs due to the additional test costs for those without an initial alteration detected.
- DNA-only sequencing is both more costly and the least effective option (i.e., detects the fewest number of actionable alterations), as patients with RNA fusions not identified are not deemed eligible for targeted therapies.

### Table 3. Annual Costs by Testing Method

| % of Patients with RNA Fusions | DNA + RNA | DNA-only | DNA-only + Reflex RNA | Savings with DNA + RNA vs. DNA-only | Savings with DNA + RNA vs. DNA + Reflex RNA |
|---|---|---|---|---|---|
| 2.5% | $240,778 | $241,178 | $241,127 | $400 | $349 |
| 5% | $240,778 | $241,394 | $241,212 | $616 | $434 |
| 10% | $240,778 | $242,009 | $241,383 | $1,231 | $605 |
| 14% | $240,778 | $242,502 | $241,519 | $1,724 | $741 |

- As RNA fusion prevalence increased, the savings associated with DNA + RNA sequencing increased, with majority of total costs and cost-savings associated with direct medical costs (**Figure 1**).

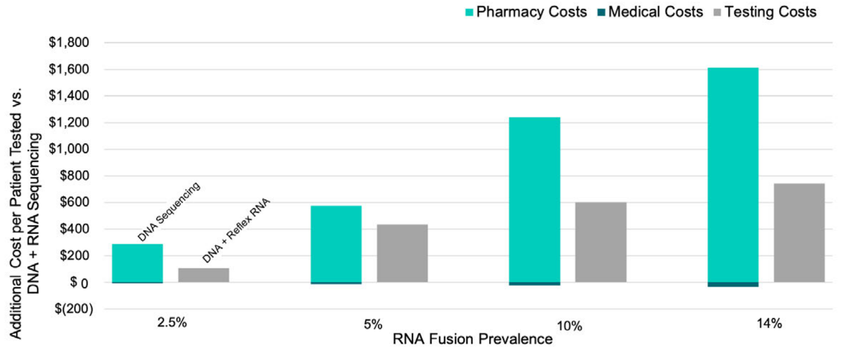
### Figure 1. Direct and Indirect Cost** Per Patient Associated with Test Choice




Within each pair of vertical bars, the first bar reflects the additional costs associated with DNA sequencing and the second bar reflects the additional cost with DNA + reflex RNA.
**Indirect costs defined as productivity losses.

- Testing costs make up a small proportion of the projected costs of treating NSCLC patients (**Figure 2**).
- Pharmacy and medical costs were equivalent when using DNA + RNA testing or when using reflex RNA testing, as patient treatments did not differ.
- The increased testing costs associated with reflex RNA testing compared with DNA + RNA rose as the prevalence of RNA fusions identified increased.
- Pharmacy and medical costs increased for patients tested with DNA-only as fusion prevalence increased.

### Figure 2. Annual Direct Medical Costs per Patient by Cost Category




Within each pair of vertical bars, the first bar reflects the additional costs associated with DNA sequencing and the second bar reflects the additional cost with DNA + reflex RNA.

### Limitations

As a potential limitation, we only considered tissue-based tests and excluded blood-based NGS testing. Additionally, there is substantial uncertainty in data inputs. This study was conducted as an exploratory analysis examining the benefits of RNA testing, however that benefit is directly tied to how common those fusions are, which differs in the literature between tests and tumor types. In a subsequent analysis, it could be interesting to assess these findings within other tumor types.

## Conclusions

- NGS tests that include upfront DNA + RNA sequencing in NSCLC patients identify those eligible for targeted therapies more efficiently, depending on the prevalence of RNA fusions.
- Upfront DNA+RNA testing reduces both costs and turn-around-time compared with initial DNA sequencing followed by reflex RNA sequencing.
- Further investigations into the advantages of RNA sequencing are warranted.

### References

1. Bewicke-Copley F et al. Applications and analysis of targeted genomic sequencing in cancer studies. Comput Struct Biotechnol J. 2019;17:1348-1359.
2. NCCN Guidelines®: Non-Small Cell Lung Cancer. Published online September 2, 2022.
3. Chakravarty D et al. Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion. J Clin Oncol. 2022;40:1231–1258.
4. Michuda J et al. Use of clinical RNA-sequencing in the detection of actionable fusions compared to DNA-sequencing alone. J Clin Oncol. 2022;40:3077–3077.
5. Hu T et al. Next-generation sequencing technologies: An overview. Human Immunology. 2021;82(11):801-811.
6. Kerr KM et al. The evolving landscape of biomarker testing for non-small cell lung cancer in Europe. Lung Cancer. 2021;154:161-175.
7. Benayed R et al. High yield of RNA sequencing for targetable kinase fusions in lung adenocarcinomas with no mitogenic driver alteration detected by DNA sequencing and low tumor mutation burden. Clin Cancer Res. 2019;25(15):4712-4722.
8. White T et al. Analytic validation and clinical utilization of the comprehensive genomic profiling test, GEM ExTra®. Oncotarget. 2021;12(8):726-739.
9. Centers for Medicare and Medicaid Services. Clinical Laboratory Fee Schedule [Internet]. 2022.
10. Wolters Kluwer. Price Rx [Internet]. 2022. Available from: https://pricerx.medispan.com/.
11. Zheng Z et al. Annual Medical Expenditure and Productivity Loss Among Colorectal, Female Breast, and Prostate Cancer Survivors in the United States. J Natl Cancer Inst. 2016;108:djv382.
12. National Cancer Institute. SEER*Explorer Application [Internet].
13. Huang RSP et al. Landscape of Biomarkers in Non-small Cell Lung Cancer Using Comprehensive Genomic Profiling and PD-L1 Immunohistochemistry. Pathol Oncol Res POR. 2021;27:592997.
14. Haslam A et al. Updated estimates of eligibility for and response to genome-targeted oncology drugs among US cancer patients, 2006-2020. Ann Oncol. 2021;32:926–932.
15. Physicians' Fee and Coding Guide. ATLANTA: InHealth Professional Services; 2021.
16. U.S. Bureau of Labor Statistics. CPI Inflation Calculator [Internet]. US Bur. Labor Stat. CPI Inflat. Calc. 2022.
17. Reyes C et al. Cost of Disease Progression in Patients with Metastatic Breast, Lung, and Colorectal Cancer. The Oncologist. 2019;24:1209–1218.
18. Ting J et al. Productivity losses under various second-line recurrent or metastatic cervical cancer treatment scenarios in the United States. 2022.

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