PRECISION MEDICINE

Budget Impact Analysis of Comprehensive Genomic Profiling in Patients With Advanced Non–Small-Cell Lung Cancer

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PURPOSE This study assessed the economic impact of increased use of comprehensive genomic profiling (CGP) versus conventional testing strategies among patients with advanced non–small-cell lung cancer (aNSCLC) from a US commercial health plan perspective.

METHODS A decision analytic model was developed to estimate the incremental benefits and costs across testing methodologies (CGP *v* non-CGP), as well as across sample types (tissue-based and liquid-based), for patients with newly diagnosed aNSCLC. Model outcomes included total direct costs, testing costs, and per member per month budget impact. Secondary model outcomes included the number of patients needed to test with CGP to add 1 life-year, and the number of patients needed to test with CGP to treat one individual with a biomarker-matched therapy.

RESULTS In a hypothetical 2,000,000-member health plan, 790 members were estimated to have incident aNSCLC; 609 underwent molecular diagnostic testing with 122 (20%) tested with CGP (109 tissue-based and 13 liquid) in the base-case. An increase in CGP from 20% to 30% (an additional 61 patients tested with CGP) was associated with 3.11 additional life-years gained and a $0.01 in US dollars per member per month budget impact. Approximately 19.6 patients would need to be tested with CGP versus non-CGP to add one life-year and 5.9 patients would need to be tested with CGP to treat at least one patient with a biomarker-matched therapy.

CONCLUSION An increase in CGP from 20% to 30% among patients with aNSCLC undergoing molecular diagnostic testing was associated with modest budget impact, most of which was attributable to prolonged survival associated with increased use of more effective treatments.

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INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality in men and women in the United States.[1] Non–small-cell lung cancer (NSCLC) accounts for approximately 84% of lung cancers,[2,3] with the majority of NSCLC (79%) presenting as advanced disease (stages IIIB or regional and IV or distant).[4] In the United States, the cost of caring for patients with lung cancer was estimated to be $14.2 billion in 2018,[5] projected to be $18.8 billion US dollars in 2020,[6] and estimated to be double the 2020 estimate by 2040.[7] Advanced NSCLC (aNSCLC) can be classified by actionable oncogenic drivers such as *EGFR*, *ALK*, *ROS1*, *BRAF*, *NTRK*, *HER2*, *MET*, *RET*, and *KRAS* alterations.[8] Many patients (50%-69%) could harbor these actionable driver alterations.[9,10] Identifying these genomic alterations is crucial for making optimal treatment decisions because the growing number of effective therapies that target driver oncogenes is continuously changing the paradigm for aNSCLC treatment. Target-specific therapies have the ability to significantly improve response to treatment and progression-free survival (PFS) compared with therapeutic regimens that do not target a specific alteration.[9,11-16]

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines) recommends broad molecular profiling in eligible patients with metastatic NSCLC with the goal of identifying rare driver mutations that may be actionable via an approved therapeutic or clinical trial.[8] The NCCN Guidelines for NSCLC provide recommendations for certain individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays or commercial laboratories. Comprehensive genomic profiling (CGP) is a next-generation sequencing approach that detects novel and known variants of the four main classes of genomic alterations and genomic signatures in tumor tissue or circulating tumor DNA (ctDNA) to provide prognostic, diagnostic, and predictive insights that inform treatment decisions for individual patients across all cancer types.

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Most non–small-cell lung cancers present as advanced disease that can be classified by actionable oncogenic drivers. Identifying genomic alterations is critical for making treatment decisions. We address the value of using comprehensive genomic profiling (CGP) versus non-CGP testing to identify genomic alterations and to match treatment within the context of a US commercial health plan.

Knowledge Generated

Compared with non-CGP approaches, CGP provides more information to guide treatment decisions at a modest increased cost; testing costs were < 1% of the total cost of care in base-case scenarios. Shifting to CGP increased the use of targeted therapies and reduced the use of chemoimmunotherapies, affording a more efficient use of resources.

Relevance

CGP provides an option for efficient identification of comprehensive molecular information that can be used to inform appropriate treatment decisions with minimal increased costs.

Non-CGP molecular diagnostic testing can include tissue-based panel tests for known NSCLC genomic alterations, single-gene tissue-based, or ctDNA-based hotspot tests (eg, *EGFR* and *ALK*) that are often used sequentially. Sequential testing approach with hotspot or single-gene assays is time consuming, limits the number of alterations identified, and frequently leads to tissue exhaustion. This approach may put patients at risk for unnecessary repeat biopsies or suboptimal care when tissue is unavailable for complete testing.[17,18] Recent advancement of liquid blood based biopsies that identify biomarkers in ctDNA has expanded opportunities for patients to be treated with biomarker guided therapies, particularly for nearly one fifth of patients with cancer who do not have tissue available for any type of testing.[19-22]

As a therapeutic approach to treatment of patients with cancer, precision oncology continues to grow.[23-25] Advancements in the technology of CGP have kept ahead of the expansion of biomarker-matched treatment options, however, for patients with aNSCLC, there are multitude of targeted therapeutic options are available and expensive chemoimmunotherapy combinations are considered in the absence of biomarkers. Questions about the costs and benefits of precision medicine, and the implications of using CGP versus other testing strategies, remain. This study evaluated the budget impact to a US commercial health plan of an increase in the use of CGP versus non-CGP approaches to testing among patients with aNSCLC. The analysis expanded on the existing literature by specifying that efficacy and costs associated with targeted therapy be matched to the specific alterations that were identified, and for patients to be treated with biomarker-matched immunotherapy based on tumor mutational burden and programmed death-ligand 1 (PD-L1) status.

METHODS

Model Overview and Design

A decision analytic model assessed a cohort of newly diagnosed patients with aNSCLC undergoing molecular diagnostic testing in the first-line setting from a US commercial payer perspective. The model population was based on a hypothetical 2-million-member health plan with an age and sex distribution matched to the 2016 US population.[26] The model compared a CGP-based testing approach with non-CGP testing approach to guide first-line treatment for patients with aNSCLC. The model compared the overall survival (OS) and cost of care associated with two hypothetical testing scenarios representing an absolute change in the CGP-based testing rate among all patients with aNSCLC undergoing testing: (1) 20% CGP testing (using FoundationOne CDx or FoundationOne Liquid CDx) and 80% testing with a mix of other conventional single-gene assay and non-CGP next-generation sequencing-based hotspot testing technologies (non-CGP testing)[27]; versus (2) 30% CGP testing and 70% non-CGP testing. Across scenarios, the overall rate of testing was unchanged, and testing in both the CGP and non-CGP groups was further distinguished across sample types (tissue or liquid). The model time horizon was based on episodes of care; the cohort was followed from their initial first-line therapy across their OS and included subsequent lines of therapy. The model was developed in Microsoft Excel 2016 (Redmond, WA).

Model Inputs

Patient population. Age-specific and sex-specific incidence rates were derived from the National Cancer Institute SEER Program and were applied to the US Census Bureau's national population projections to estimate the number of patients with aNSCLC in the hypothetical health plan (Table 1).

Alterations and Testing

Alteration frequencies were provided from Foundation Medicine's FoundationCore database; the data sample contained 9,775 patients sequenced through the year 2018 for which PD-L1 testing results were available. Frequencies of detected alterations by testing method are

TABLE 1. Model Inputs

Parameter	Value		Source
Health plan characteristics			
Patient population in health care plan, No.	2,000,000		Assumption
Men < 65 years, %	42		US Census Bureau[26]
Men ≥ 65 years, %	7		US Census Bureau[26]
Women < 65 years, %	42		US Census Bureau[26]
Women ≥ 65 years, %	9		US Census Bureau[26]
Epidemiology			
NSCLC annual incidence (per 100,000)			
Men < 65 years	18.1		US Census Bureau[26] Howlader et al[28]
Men ≥ 65 years	269.8		US Census Bureau[26] Howlader et al[28]
Women < 65 years	17.2		US Census Bureau[26] Howlader et al[28]
Women ≥ 65 years	198.8		US Census Bureau[26] Howlader et al[28]
Advanced NSCLC at diagnosis, %	79		SEER[4]
Stage IIIb	24		SEER[4]
Stage IV	55		SEER[4]
Testing, %			
Patients undergoing tissue-based testing	69		Gondos et al[27]
Patients undergoing liquid testing (required)[a]	8		Madison et al[29]
CGP testing—scenario 1, current use	20		Gondos et al[27]
CGP testing—scenario 2, increased use	30		Assumption
Fine-needle biopsy	43		Shinde et al[30]
Open biopsy	2		Shinde et al[30]
Bronchoscopy	56		Shinde et al[30]
Treatment and survival, months	OS	PFS	
Matched targeted therapy			
Tyrosine kinase inhibitors (*EGFR*)	27.6	12.6	Paz-Ares et al[31] Rosell et al[32] Ramalingam et al[33] Soria et al[34]
ALK inhibitors	26.3	20.8	Gadgeel et al[35] Camidge et al[36] Soria et al[37] Peters et al[38]
ALK inhibitors (targeting *ROS1*)	24.0	19.3	Lim et al[39] Shaw et al[40]
Dabrafenib plus trametinib (*BRAF*)	24.6	10.9	Planchard et al[41]
Ado-trastuzumab emtansine (*HER2*)	16.4	5.0	Li et al[42]
MET inhibitor	8.1	8.2	Awad et al[43] Wolf et al[44]
NTRK inhibitors	21.3	15.8	Drilon et al[45]
RET inhibitor	7.6	8.3	Gautschi et al[46] Drilon et al[47]
Immunotherapy			
TMB-related IO	11.2	5.7	Hellmann et al[48]
PD-L1–related IO	16.7	5.4	Mok et al[49]

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TABLE 1. Model Inputs (Continued)

Parameter	Value		Source
Nonmatched targeted therapy	10.3	4.8	Assumption
Chemoimmunotherapy	19.2	10.0	Socinski et al[50] Gandhi et al[51] Langer et al[52]
Chemotherapy	10.3	4.8	Scagliotti et al[53]
Clinical trial	10.3	4.8	Scagliotti et al[53]
Costs, $			
CGP tissue-based test	3,500.00		CMS[54]
CGP conventional liquid test	3,500.00		CMS[54]
Non-CGP tissue-based test[b]	598.15		CMS[54]
Non-CGP conventional liquid test[c]	324.58		CMS[54]
Fine-needle biopsy	157.32		CMS[54]
Open biopsy	866.04		CMS[54]
Bronchoscopy	371.66		CMS[54]
Cost associated with liquid testing[d]	180.72		CMS[54]
Monthly medical service costs			
Targeted therapy	1,659.90		Graham et al[55]
Immunotherapy	3,924.13		Huang et al[56]
Chemotherapy	5,886.19		Huang et al[56]
No drug treatment	3,911.78		Guerin et al[57]
Matched targeted therapy monthly cost[e,f]			
Tyrosine kinase inhibitors (*EGFR*)	13,587.75		Micromedex Red Book[58]
ALK inhibitors	19,503.00		Micromedex Red Book[58]
ALK inhibitors (targeting *ROS1*)	19,503.00		Micromedex Red Book[58]
Tafinlar plus Mekinist (*BRAF*)	23,562.00		Micromedex Red Book[58]
Ado-trastuzumab (*HER2*)	6,064.57		Micromedex Red Book[58]
MET inhibitor	14,250		Micromedex Red Book[58]
NTRK inhibitors	40,080.00		Micromedex Red Book[58]
RET Inhibitor	23,896		Micromedex Red Book[58]
Immunotherapy monthly cost[e]			
TMB-related IO	17,800.03		Micromedex Red Book[58]
PD-L1–related IO	13.927.29		Micromedex Red Book[58]
Nonmatched targeted therapy monthly cost[g]	12,881.04		Assumption
Chemoimmunotherapy monthly cost	24,776.40		Micromedex Red Book[58]
Chemotherapy monthly cost[h]	9,325.71		Micromedex Red Book[58]
Clinical trial monthly cost[i]	10,100		Reitsma et al[59]
AEs (grade 3+)			
Biopsy-related AE	32,999.28		HCUP NIS[60]
Neutropenia	13,832.07		HCUP NIS[60]

(Continued on following page)

TABLE 1. Model Inputs (Continued)

Parameter	Value	Source
Anemia	7,174.55	HCUP NIS[60]
Thrombocytopenia	10,768.41	HCUP NIS[60]
Diarrhea	7,789.02	HCUP NIS[60]
Pneumonia	12,046.64	HCUP NIS[60]

Abbreviations: AE, adverse event; CGP, comprehensive genomic profiling; CMS, Centers for Medicare and Medicaid Services; CPT, Current Procedural Terminology; HCUP, Healthcare Cost and Utilization Project; IO, immuno-oncology; NIS, national inpatient sample; NSCLC, non–small-cell lung cancer; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RCTs, randomized controlled trials; TMB, tumor mutation burden; WAC, wholesale acquisition cost.

[a]The proportion of patients receiving liquid testing reflects those patients who are unable to undergo tissue-based testing and receive liquid testing.

[b]Cost of a single non-CGP test was calculated based on a mix of potential genomic tests. Sixty percent were assumed to be panel tests for all known NSCLC genomic mutations (CPT code: 81445), 20% were assumed to be tests for *EGFR* only (CPT code: 81235), and 20% were assumed to be tests for *ALK* only (CPT code: 88374). The cost of a single PD-L1 test (CPT code: 88360) multiplied by the proportion of patients who undergo this test was added.

[c]Cost based on the cost of single *EGFR* test; either cobas *EGFR* or OncoBEAM *EGFR*/*BRAF*.

[d]Cost associated with liquid biopsy is assumed to be the cost of a venipuncture, age 3 years or older, necessitating the skill of a physician or other qualified health care professional, for diagnostic or therapeutic purposes (CPT code: 35410), as well as the cost of a 40-minute physician office visit (CPT code: 99215).

[e]Monthly cost for targeted therapy and immunotherapy is calculated as the sum of the monthly costs for treatments listed within the treatment type, weighed by the prevalence of the alterations for which a given treatment is the matched treatment.

[f]WAC/mg was calculated by averaging across all available WAC prices for a given drug using Red Book ReadyPrice. Where applicable, patient's weight was assumed to be 75 kg and patient's body surface area was assumed to be 1.7 m^2.[61] Dose and length of cycle is based on prescribing information available for each drug.

[g]Nonmatched targeted therapy cost was calculated as an average of the monthly costs of bevacizumab and ramucirumab.

[h]Chemotherapy cost was calculated as the monthly cost of pemetrexed and monthly administration costs.

[i]Clinical trial drug costs were assumed to be 25% of the cost of chemotherapy (including administration costs). The assumption was based on the estimate that 50% of all trials would be RCTs, and 50% of the patients in RCTs would be on control arms and receive chemotherapy.

shown in Appendix Table A1. Rates of testing were sourced from the published literature. Based on published data, 77% of patients received diagnostic testing (69% tissue-based testing and 8% liquid-based testing reflecting those unable to undergo tissue-based testing).[27,29] We assumed that for tissue-based non-CGP, 60% were assumed to undergo panel tests for all known NSCLC genomic alterations, 20% were assumed to be tested for EGFR only, 20% were assumed to be tested for *ALK* only, and 67% were assumed to undergo PD-L1 testing.[27] For testing via non-CGP liquid-based genomic profiling, patients were assumed to undergo testing with a mix of liquid *EGFR* and *BRAF* tests (Appendix Table A2).

Treatment

Patients were matched to therapy classes based on their respective molecular diagnostic test results. Therapy classes included (1) targeted therapies associated with the identified biomarker, (2) matched immunotherapies associated with the identified biomarker, (3) nonmatched targeted therapies, (4) chemoimmunotherapy combinations, (5) chemotherapy, (6) clinical trials, and (7) no drug treatment.

Duration of therapy was based on reported PFS and OS. Among drug classes where multiple therapies were approved and available, median PFS and OS estimates were averaged across the class.

Costs

This analysis considered costs for diagnostic testing, biopsies, blood draws, first-line treatment, administration, health resource utilization (HRU), and biopsy-related and drug-related adverse events (AEs). Costs were inflation-adjusted to 2018 US dollars (USD). Costs were sourced from the Centers for Medicare and Medicaid Services' Clinical Diagnostic Laboratory and Physician Fee Schedules,[54] published literature, and inpatient care costs as reported by the national inpatient sample (Table 1).

Costs for CGP and non-CGP were determined using Current Procedural Terminology and Healthcare Common Procedure Coding System (HCPCS) codes. Cost of a single non-CGP test was calculated based on a mix of potential genomic tests; 60% were assumed to be panel tests for all guideline-recognized NSCLC molecular targets, 20% were assumed to be tests for *EGFR* only, and 20% were assumed to be tests for *ALK* only. The cost of a single PD-L1 test multiplied by the proportion of patients undergoing this test was added.

Distribution of biopsy testing was extracted from the patient distribution in the study by Shinde et al.[30] Biopsy costs were

based on Current Procedural Terminology codes for each procedure, whereas liquid biopsy costs were assumed to be the cost of a venipuncture plus the cost of a 40-minute physician office visit.[54] Percutaneous biopsy costs included those receiving a fine-needle biopsy and those receiving an open biopsy including surgical biopsy and other biopsy.

Monthly HRU costs included outpatient visits, interventions, and unplanned hospitalizations unrelated to AEs. HRU costs were extracted from clinical trials where data were readily available and when the clinical trial was representative of a typical clinical trial for lung cancer therapy. For targeted therapy, monthly HRU costs were sourced from the observed utilization in the Lux-Lung 3 trial.[55] For the immunotherapy and chemotherapy arms, monthly HRU costs were sourced from observed utilization in KEYNOTE-024 trial.[56] For patients who did not receive treatment with anticancer drugs, monthly HRU costs were sourced from an analysis of administrative claims data on patients with aNSCLC after they had discontinued drug treatment.[57] Targeted therapy monthly HRU costs were assigned to both matched and nonmatched therapy. In the model, chemotherapy monthly HRU costs were assigned to both matched and nonmatched clinical trials and chemo-immunotherapy regimens.

Anticancer drug and administration costs in the analysis included both index therapy and treatments in subsequent lines of therapy. After progression, patients could be allocated to a subsequent line of therapy depending on their first-line treatment.

Cost of therapy was calculated based on clinical dosing, average wholesale acquisition cost, and the duration of therapy. Cost per milligram was calculated by averaging across the available wholesale acquisition costs for a given drug using Red Book ReadyPrice.[58] Where applicable, patient's weight was assumed to be 75 kg and patient's body surface area was assumed to be 1.7 m^2.[61] Dose and length of cycle was based on prescribing information available for each drug. Monthly costs for drugs in clinical trials were assumed to be 25% of the monthly costs of chemotherapy (including administration costs), based on the assumption that half of the trials are single-arm studies of an investigational agent, for which drug costs are covered by the sponsor, and the other half include random assignment to a standard of care arm in which drug costs are passed on to the payer.[59] Monthly costs for the targeted therapy and immunotherapy arms were calculated as the sum of the monthly costs for treatments listed within the treatment type, weighted by the prevalence of the alterations for which a given treatment is the matched treatment.

Outcomes

Annual incremental benefits, the total, and the per member per month (PMPM) budget impact associated with the increased use of CGP testing were estimated. Benefits and costs were assessed across sample types (tissue-based *v* liquid-based CGP, and non-CGP). The number needed to test with CGP versus non-CGP to add 1 life-year, and the number needed to test with CGP versus non-CGP to place one individual on biomarker matched therapy were also estimated.

RESULTS

The results are presented in Table 2 and Figure 1. In a health plan with 2 million covered lives, 790 patients were

TABLE 2. Incremental OS and Budget Impact With an Increase in CGP Testing

Outputs	Current Use (20%)	Increase in CGP (30%)	Difference
Testing patterns			
Patients with NSCLC, No.	1,000	1,000	—
Patients with aNSCLC, No.	790	790	—
Patients undergoing molecular diagnostic testing, No.	609	609	—
Patients undergoing tissue-based CGP	109	164	55
Patients undergoing liquid-based CGP	13	19	6
Total life-years	844.1	847.2	3.11
Total costs, per patient with any molecular diagnostic testing	$325,548	$325,753	$205
Diagnostic testing	$1,987	$2,186	$199
Medical-related	$77,582	$77,328	–$253
Anticancer therapies	$237,403	$237,724	$321
Matched therapy	$71,970	$74,350	$2,380
Nonmatched therapy	$165,434	$163,375	–$2,059
Biopsy	$6,322	$6,279	–$42
AE-related	$2,254	$2,235	–$20

Abbreviations: AE, adverse event; aNSCLC advanced non–small-cell lung cancer; CGP, comprehensive genomic profiling; NSCLC, non–small-cell lung cancer; OS, overall survival.

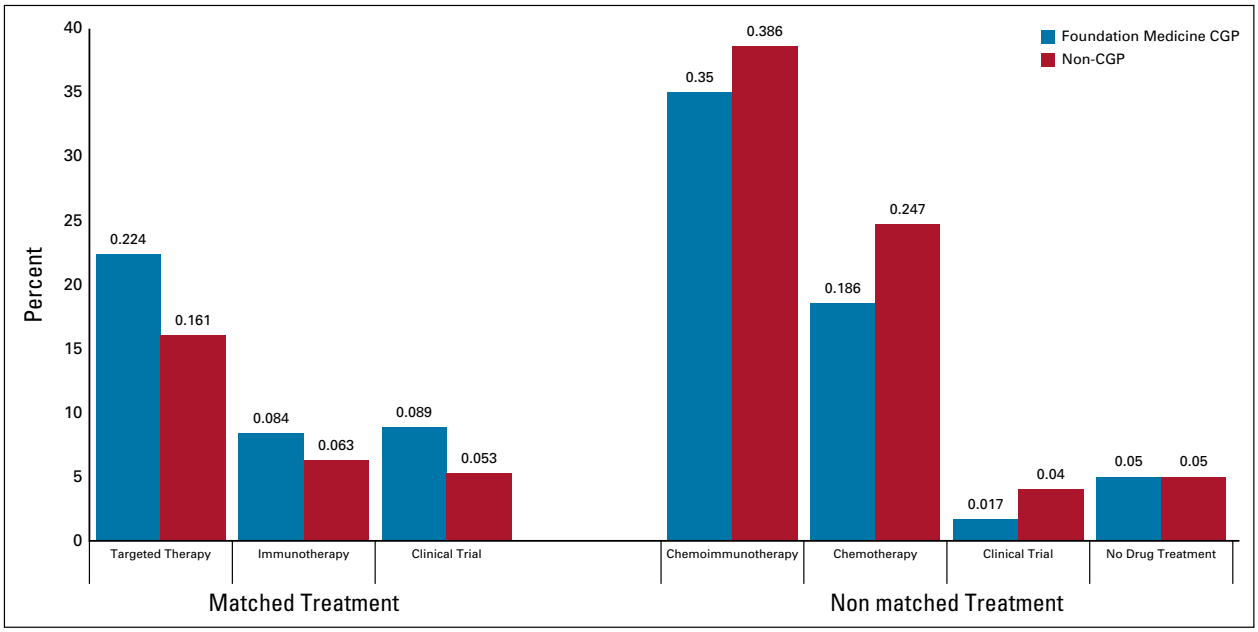

FIG 1. Treatment distribution by category after molecular diagnostic testing. CGP, comprehensive genomic profiling.

expected to be newly diagnosed with aNSCLC in year 1. Of those, 609 were estimated to undergo molecular diagnostic testing (545 tissue-based and 64 liquid-based). In the base-case analysis, 122 patients underwent CGP (109 tissue-based and 13 liquid-based), per patient drug costs were estimated to be $237,403, and the total cost of care was estimated to be $325,548. With an increase in CGP from 20% to 30%, 183 patients would be tested, and per patient drug costs and total cost of care were estimated to be $237,724 (+$321) and $325,753 (+$205), respectively. An increase in CGP among those tested, from 20% to 30% (an additional 61 patients tested with CGP), was associated with $0.005 PMPM budget impact. In the base-case analysis, 19.6 patients would need to be tested with CGP versus non-CGP methods to add 1 life-year, and 5.9 patients would need to be tested with CGP to treat one individual with a biomarker-matched, first-line therapy. Expanding CGP availability also contributed to an additional 3.11 life-years (3.02 attributed to tissue-based testing and 0.1 attributed to liquid-based testing).

DISCUSSION

Genomically matched therapy has become the standard of care for treating patients with aNSCLC. Evidence on the economic implications of using CGP versus alternative strategies is accruing and will continue to inform approaches for addressing goals of improving outcomes for the advanced cancer population and improving the quality and experience of care in the face of the inevitable constraints imposed by health care budgets.[62] Broader adoption of CGP is expected to improve the identification of genomic alterations and identification of patients appropriate for treatment with targeted therapy in real-world treatment settings.

Modeling results demonstrated that increased testing with CGP yielded additional benefit for patients. In a health system with 2 million covered lives, 1 additional life-year is expected to be gained with 19 additional patients with aNSCLC tested with CGP. Similarly, testing six additional patients is expected to result in one additional patient being treated with a biomarker-matched therapy that is most likely to be effective. With a greater proportion of patients matched to targeted therapies, the model predicts a shift among treated patients from nontargeted chemo-immunotherapy combinations to targeted therapies.

Compared with testing strategies using non-CGP, which may miss identification of less common alterations, CGP provides physicians with more information to guide treatment decisions. Broad molecular profiling tests for all alterations recommended by NCCN Guidelines, as well as for alterations such as *NTRK,* which may have a tumor-agnostic therapy available or enable clinical trial eligibility. Efficient analysis and identification of alterations in all guideline-recommended genes for patients with NSCLC is key to identifying the targeted therapy likely to be the most effective available treatment. As physicians are provided with comprehensive molecular information to inform appropriate treatment decisions with little or no need for repeat biopsy, the patient experience is expected to be better.

Expanding use of CGP from 20% to 30% resulted in a relatively small incremental budget impact of $0.005 PMPM. The costs associated with expanding CGP were modest—a total cost of $205 per patient over the model time horizon. As expected, the estimated increase in survival was associated with a slight increase in drug therapy costs on a per patient basis (+$321). Targeted therapies

were associated with lower medical service expenditures than other categories of drug therapy; the increase in costs associated with testing was offset by this reduction in costs associated with medical services (–$253). Although total costs increased as a result of more testing with CGP, the overall costs associated with testing ($2,186, Table 2) were < 1% of the total cost of care ($325,753, Table 2) and were offset by a reduction in HRU associated with more treatment with targeted therapy. In this analysis, a shift from chemoimmunotherapy combinations and target-agnostic therapies to more effective and tolerable targeted therapeutic options afforded more efficient use of the drug and overall spend, as evidenced by an offset in testing costs. Reducing use of target agnostic therapies, lowering cost of care, and increasing survival all because of the increased use of CGP are all consistent with the goals of the Institute for Healthcare Improvement Triple Aim.[63]

Although they used different methodologic approaches, three other recent health economic studies assessed the value of CGP compared with non-CGP in the context of treatment of aNSCLC. A recent cost-effectiveness analysis (CEA) from the US perspective estimated a gain of approximately 0.06 life-years at a cost of $9,000 per patient for CGP.[64] In comparison, our model estimated a gain of approximately 0.05 life-years per patient at an additional cost of approximately $2,000. Although the life-years gained in each model were similar, the incremental costs in the CEA model were greater; however, within the CEA model, more patients (relatively) were diverted to immunotherapy following CGP.[64] Costs for immunotherapy were much greater, which could help explain the difference in results. The second CEA that we identified was developed from the Brazilian payer perspective; thus, it is difficult to compare and contrast costs directly.[65] In addition, the two CEA models were state-transition models; consequently, we would caution against comparison of the results of our model. In the third economic study that we identified, a budget impact analysis was developed from the Canadian perspective and used a model structure similar to that used in our analysis.[66] However, because the health system is different, a direct comparison with the results of our modeling analysis cannot be made. Furthermore, the results from the Canadian budget impact analysis were not presented at the individual level; thus, any comparison of life-years gained was not feasible. In all three studies, CGP was associated with a gain in life-years. The relatively small gain in life-years identified in the two CEAs and our model results were similar and could be attributed to poor disease prognosis even with use of the best treatment options.

The analysis presented in this study is novel in its inclusion of liquid-based and tissue-based CGP. Our analysis concluded that an increased liquid-based CGP is expected to have two primary benefits for patients. First, liquid biopsy provides a CGP option that may result in fewer AEs and subsequently reduced costs among patients who have insufficient tissue for molecular testing or who are unable or unwilling to tolerate the risk of repeat biopsy. There are still some patients unable to undergo any molecular testing because of lack of tissue; these patients would most likely be treated with nontargeted treatment options, by default if liquid-based testing was not available. Second, in a population with access to liquid-based CGP, clinical benefit may result from a decrease in time to treatment initiation with the reduction in time required to procure tissue via biopsy or pathology request. The added benefit of liquid-based CGP access to these patients is anticipated to result in allocation of more patients to targeted therapies. Taken together with the results of this analysis, the availability of liquid-based and tissue-based CGP across the population was associated with only a modest budget increase but resulted in high-value care through substantial increases in PFS and OS.

Limitations associated with the current study presented here include data availability, model and testing assumptions, and assumptions about outcome measures. First, assumptions were used as data were not available for every model input. Where assumptions were required, clinical and expert opinions were used, which could affect the generalizability of the results. Incorporating real-world data if it becomes available should improve the generalizability and robustness of the results. Second, we assumed that patients had unrestricted access to listed therapies based on NCCN Guidelines. Third, this model does not account for all benefits. For example, if a patient tested positive for an *EGFR* or *ALK* mutation, then immunotherapy would not be recommended. Comprehensive testing provides this information. However, the model was not designed to capture the frequency of therapy avoidance in alignment with guideline recommendations.[8] Fourth, the model does not include serial testing. That is, each patient in the analysis was assumed to only be tested one time. Finally, patients for whom an actionable biomarker is not identified are assumed to receive the average efficacy of nonmatched treatments as reported in clinical trials. To the extent that patients have an actionable alteration but are not identified as having one, these patients may have truly different outcomes, which are not currently accounted for in the model.

Although increases in first-line therapy costs are expected to occur with additional patients being matched to target-specific therapy, cost-offsets are expected because of fewer patients being treated with biomarker-agnostic immunotherapy, and lower costs associated with medical services and AE-related treatment. Allowing for CGP via liquid biopsy compared with tissue-based testing provided additional benefit for patients with minimal budget impact. CGP diagnostic testing improves identification of genomic alterations in patients with aNSCLC, enabling improved patient selection for targeted therapies. An increase in molecular diagnostic testing with CGP can help inform treatment

decisions and contribute to better therapeutic decision making for patients with aNSCLC. Thus, the increase in CGP was associated with clinical benefit and a relatively small increase in overall costs, suggesting that CGP can help lead to an overall improvement in the quality of care for patients with aNSCLC.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

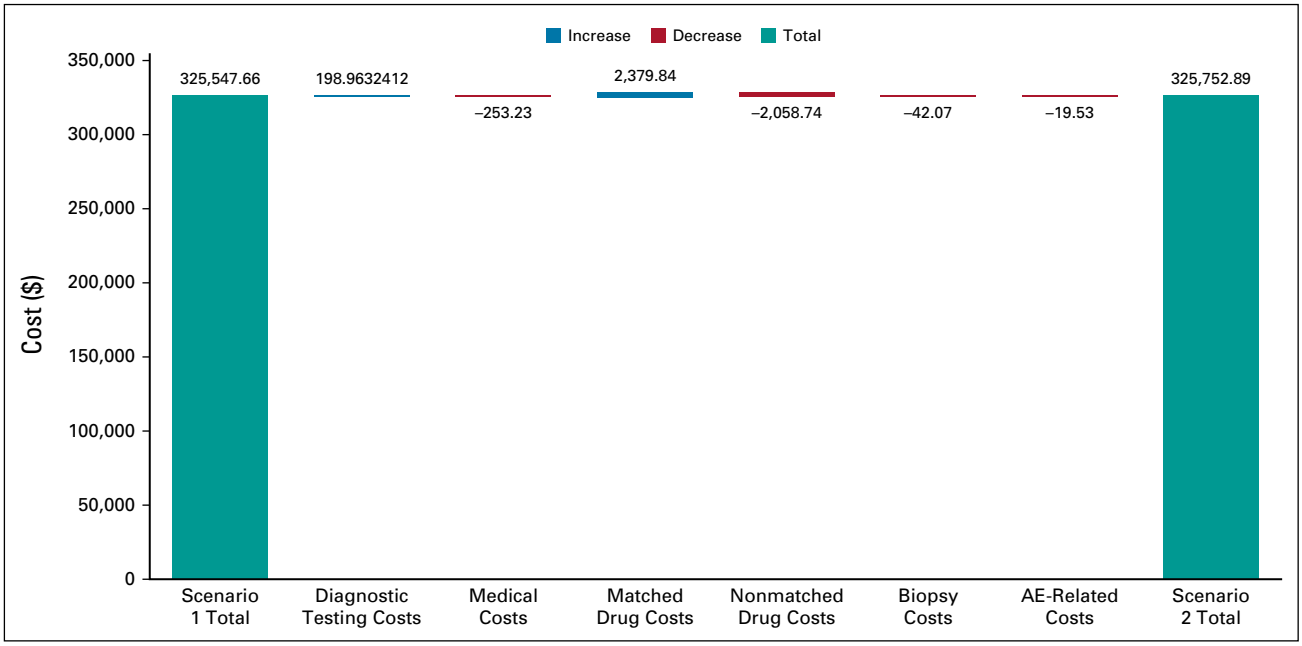

FIG A1. Incremental cost changes from scenario 1 to scenario 2. AE, adverse event.

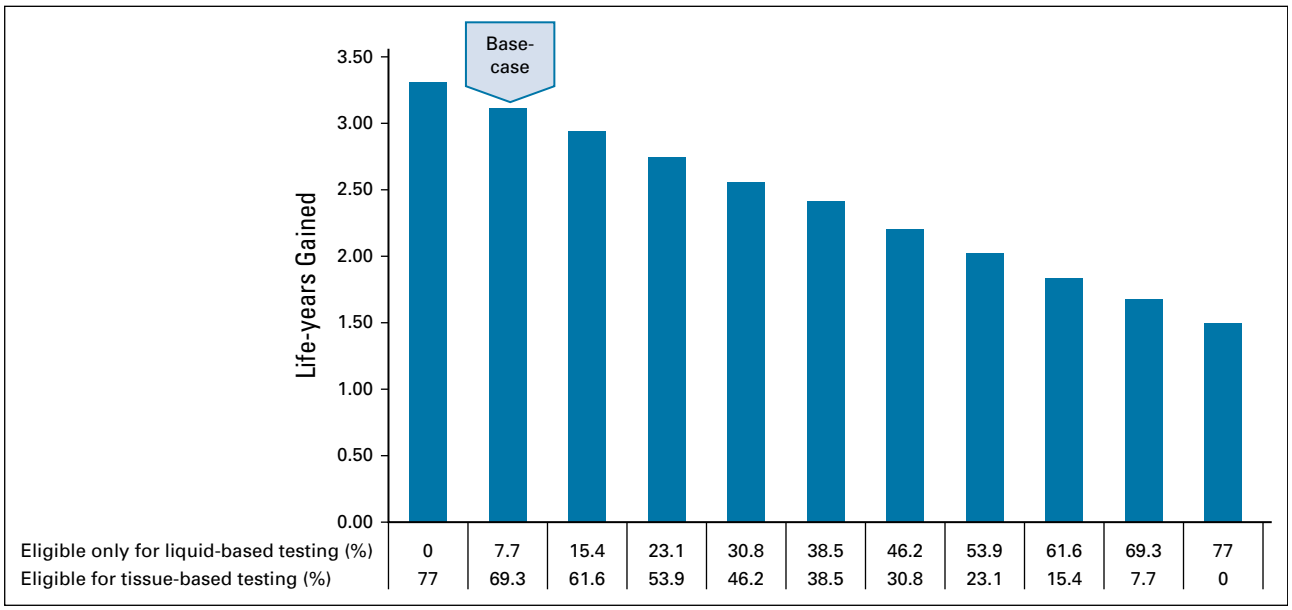

FIG A2. Total life-years gained from scenario 1 to scenario 2, given change in testing modality. This figure shows the change in total life-years as the overall proportion of testing eligibility changes. The base-case population testing rate of 77% was fixed, and the eligibility within that testing rate was adjusted. As more patients are transitioned to being eligible only for liquid-based testing (using CGP or non-CGP), model estimates that total life-years gained will decrease. This result is because of fewer patients being treated with targeted therapy. CGP, comprehensive genomic profiling.

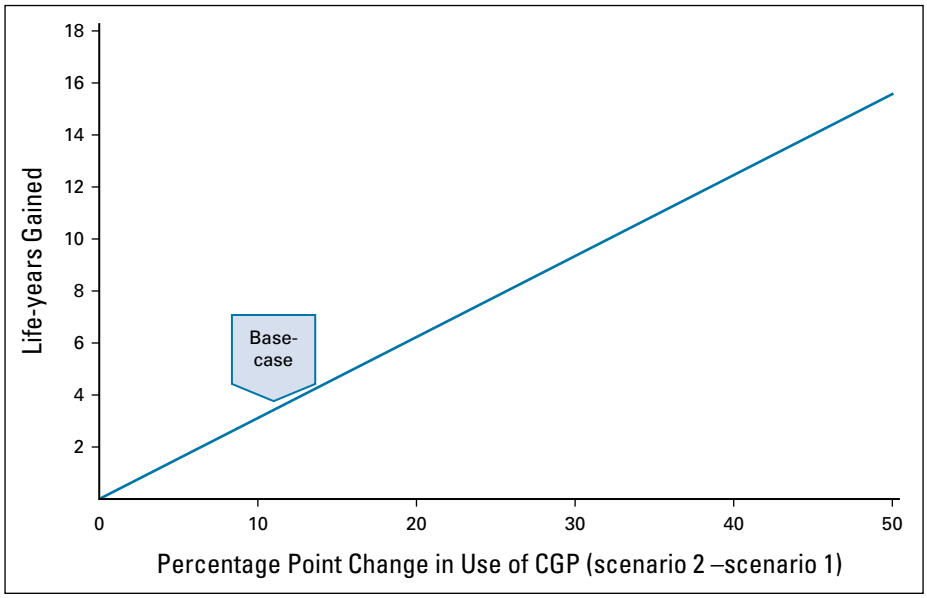

FIG A3. Incremental total life-years gained from given percentage point change in use of CGP. This figure shows total life-years gained given an incremental increase in CGP (from 20% in the base-case). Specifically, the shares of tissue-based and liquid-based testing were held constant to assess the impact of increasing the share of CGP in scenario 2. Increasing CGP can lead to an increase in life-year gains. CGP, comprehensive genomic profiling.

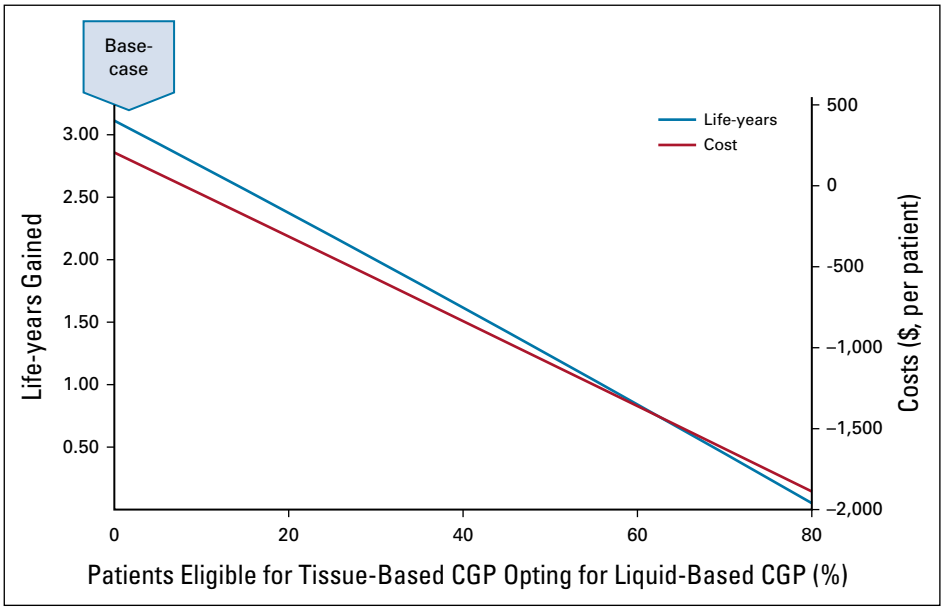

FIG A4. Total life-years gained and incremental costs per patient given opt-in to liquid-based CGP. This figure shows the outcome associated with increasing the share of liquid-based CGP. All testing rates were held constant. In the base-case model, we assumed any patient who was eligible for tissue-based CGP (eg, scenario 1 = 69% × 20% = 13.8%) would undergo testing with tissue-based CGP; no patients would have opted for liquid-based CGP who were eligible for tissue-based CGP. For patients not tested using CGP, testing rates were held constant. As more patients opt-in to liquid-based CGP, the gain in total life-years decreases, as does the incremental cost per patient. This is because of fewer patients being treated with targeted therapy. CGP, comprehensive genomic profiling.

TABLE A1. Model-Calculated Biomarker Distribution Weighted by Testing Methods Available

	CGP Variants Detected Based on Testing Rates (%)				Non-CGP Variants Detected Based on Testing Rates (%)			
Biomarker	Alteration Only	TMB (≥ 10 m/Mb)	PD-L1–Positive (≥ 1%)	TMB (≥ 10 m/Mb) and PD-L1–Positive	Alteration Only	TMB (≥ 10 m/Mb)	PD-L1–Positive (≥ 1%)	TMB (≥ 10 m/Mb) and PD-L1–Positive
EGFR	9.4	1.1	4.5	0.9	8.8	0.0	4.3	0.0
ALK	1.1	0.1	1.0	0.0	0.8	0.0	0.9	0.0
ROS1	0.3	0.1	0.3	0.0	0.2	0.0	0.2	0.0
BRAF	1.2	0.5	0.9	0.6	1.1	0.0	0.9	0.0
NTRK	0.1	0.2	0.1	0.2	0.2	0.0	0.2	0.0
HER2	1.4	0.8	0.6	0.4	1.3	0.0	0.6	0.0
MET	1.2	0.5	1.3	0.7	0.9	0.0	1.2	0.0
RET	0.4	0.1	0.3	0.1	0.3	0.0	0.2	0.0
KRAS	3.9	2.2	2.5	2.5	3.3	0.0	3.0	0.0
TMB (≥ 10 m/Mb)	17.0	0.0	18.1	0.0	0.0	0.0	0.0	0.0
PD-L1–positive (≥ 1%)	6.8	0.0	0.0	0.0	31.6	0.0	0.0	0.0
No actionable biomarker identified	16.6	0.0	0.0	0.0	40.2	0.0	0.0	0.0

Abbreviations: CGP, comprehensive genomic profiling; PD-L1, programmed death-ligand 1; TMB, tumor mutation burden.

TABLE A2. Coverage Rates of Genomic Alteration Testing by Molecular Diagnostic Testing Type

Biomarker	CGP Tissue-Based (%)	CGP Liquid-Based (%)	Non-CGP Tissue-Based[a] (%)	Non-CGP Liquid-Based[b] (%)
EGFR	100	100	80	100
ALK	100	100	80	0
ROS1	100	100	60	0
BRAF	100	100	60	100
NTRK	100	0	60	0
HER2	100	100	60	0
MET	100	100	60	0
RET	100	100	60	0
KRAS	100	100	60	0
TMB (≥ 10 muts/Mb)	100	0	0	0
PD-L1–positive (≥ 1%)	72	0	72	0

Abbreviations: CGP, comprehensive genomic profiling; mut/Mb; mutations/megabase; NGS, next-generation sequencing; NSCLC, non–small-cell lung cancer; PD-L1, programmed death-ligand 1; TMB, tumor mutation burden.

[a]Non-CGP testing was represented as a mix of conventional and NGS-based tests for single genes and small NSCLC panels: 60% were panel tests for specific alterations within common genes (EGFR, ALK, ROS1, HER2, BRAF, MET, RET, KRAS, and NTRK); 20% were single-gene tests for alterations of EGFR; and 20% were single-gene tests for ALK. Thus, 80% are tested for EGFR, 80% are tested for ALK, and 60% are tested for alterations at the remaining loci listed above. Additionally, 72% are tested for PD-L1 status. By assumption, no additional biomarkers (eg, TMB) are tested with non-CGP testing.

[b]The base-case for liquid testing assumes that among patients receiving non-CGP testing in NSCLC, 100% will be tested for alterations in EGFR and BRAF through cobas liquid testing. Additionally, 0% of patients are tested for PD-L1–positive status or TMB status.

