Biomarkers and Molecular Profiling in Non-Small Cell Lung Cancer: An Expanding Role and Its Managed Care Implications

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Abstract

Lung cancer is the leading cause of cancer-related mortality in the world. The American Cancer Society estimated that in 2013, the disease will account for almost 159,500 deaths in the United States, or approximately 27% of all cancer deaths in the country. Lung cancer accounts for about 14% and 12% of all new cancer diagnoses in males and females, respectively, and nearly 70% of patients with lung cancer will present with locally advanced or metastatic disease at initial diagnosis. Despite evidence-based recommendations and clinical guidelines that support the utility of epidermal growth factor receptor (EGFR) mutation testing in improving targeted therapy in non-small cell lung cancer (NSCLC), the most common form of lung cancer, EGFR testing continues to be underutilized, as the procedure may cost up to $1000 and require up to 2 weeks for results. Additional research and data collection will be needed to ascertain the cost-effectiveness and role of molecular testing and targeted therapies in the management of NSCLC. This article reviews the current testing strategy and treatment guidelines, and provides a pharmacoeconomic evaluation of the use of EGFR testing to guide the management of NSCLC in today's cost-constrained healthcare environment.

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For author information and disclosures, see end of text.

Lung cancer is a highly prevalent malignancy that is associated with substantial morbidity and mortality. Histologically, it is divided into non-small cell lung cancer (NSCLC), the more common form, and small-cell carcinoma. Numerous clinical studies evaluating treatment efficacy have been conducted in the therapeutic space for NSCLC, but areas of uncertainty for the disease that continue to persist include the benefit of targeted agents in unselected and general patient populations, the value and appropriate timing of testing to guide the appropriate use of specific agents, and the optimal sequencing of agents (ie, first-line, second-line, etc).[1] In the first article in this supplement, the epidemiology, pathophysiology, and treatment options for NSCLC are examined, focusing on the epidermal growth factor receptor (EGFR).[2] This article provides an overview of the biomarkers that are associated with clinical outcomes in NSCLC and the recommendations for molecular profiling in NSCLC, as a means to effectively implement targeted therapies, individualize treatment regimens, and ensure optimal and cost-effective disease management in NSCLC.

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Biomarker Testing

The healthcare system has entered a transitional period during which clinicians and health plans are under increasing pressure to deliver the most therapeutically effective treatments—which are often the most expensive options—in the most cost-effective manner.[3,4] Strategies to help limit healthcare spending include the implementation of utilization management programs and/or cost agreements to control the prices of treatments.[3] These strategies should incorporate the results of comparative effectiveness research to provide treatment in a cost-effective manner.[4] Biomarker testing for patients with NSCLC is one strategy that may help improve cost-effectiveness. By utilizing biomarker testing judiciously, clinicians may design optimal treatment regimens for their patients with NSCLC.[1,5-7]

Many different types of methodologies are available to classify lung cancer and to determine EGFR abnormalities.[1,8-17] Tissue sampling for histology reveals the subtype of NSCLC, with adenocarcinoma being more likely to reveal the presence of EGFR and V-Ki-ras2 Kirsten rat sarcoma oncogene homolog (KRAS) mutations.[8] Although certain factors are predictive of EGFR abnormali-

ties, such as Asian ethnicity, adenocarcinoma, nonsquamous pathology, no history of smoking, and female gender, testing is necessary to ensure the presence and type of EGFR abnormality.[1,5-7] For example, EGFR mutations have been found in up to 20% to 40% of Caucasians and 40% to 50% of Asians.[9]

Tsao and colleagues examined tumor samples from patients enrolled in the BR.21 study for EGFR mutations and the number of EGFR genes to examine whether responsiveness to erlotinib and its impact on survival were associated with EGFR expression, gene amplification, or mutations. Participants in the BR.21 study had NSCLC and had previously been treated with and failed first- or second-line chemotherapy.[10,11] Tissue samples were collected from paraffin blocks or 10 to 20 unstained slides for each patient, and then tested for EGFR protein expression using immunohistochemistry through Dako EGFR PharmDx kits. Samples containing more than 10% staining were considered positive for EGFR. Specimens with cellularity of more than 50% were scraped from the slides for isolation of DNA and mutational analysis. For specimens with less tumor cellularity, enriched DNA was isolated using microdissection, then amplified with polymerase chain reaction (PCR) assays via AmpliTaq Gold and primer sets. Purified PCR products were then sequenced in both directions using a BigDye Terminator Cycle Sequencing Kit and an ABI Genetic Analyzer, and further analyzed using SeqScape software, followed by manual review. Fluorescence in situ hybridization (FISH) was performed using dual color DNA probes to determine the number of EGFR copies. The samples with a high number of copies were considered FISH-positive.[11] A total of 325 tumors were evaluated for immunohistochemistry, of which 184 (57%) were positive for EGFR, including 50% of the adenocarcinoma samples and 63% of the other samples. FISH was attempted in 221 tumors and was successful in 125 (57%) of the cases. Forty-five percent of the successful cases demonstrated high polysomy or amplification (48% of adenocarcinoma and 41% of the other samples), indicating presence of multiple EGFR genes in tumors. Mutational analysis was attempted in 197 samples, of which 110 samples yielded sufficient DNA for amplification of exons 18, 19, 20, and 21. Of these, 107 were successfully analyzed, and 24 (22%) contained 1 or more mutations. Investigators were able to amplify exons 19 and 21 in 70 of the 87 samples that did not contain sufficient material for a testing of exons 18 to 21. The net result was successful mutational analysis for 90% of the samples.[11]

Investigators found a total of 45 mutations in 40 patients. Mutations were present in 28% of samples of those with adenocarcinoma and 16% of the samples with other types of NSCLC.[11] The presence of a mutation did not correlate with the expression of EGFR or the number of copies of EGFR. Neither patient survival nor disease severity was predicted by EGFR mutation status, the number of copies of EGFR, the presence of EGFR mutations, or the status of protein expression. However, a subgroup of patients with EGFR overexpression who were treated with erlotinib demonstrated significantly longer survival than patients who had received placebo (hazard ratio [HR], 0.68; 95% confidence interval [CI] 0.49-0.95; $P = .02$). There was no survival benefit with erlotinib in patients with EGFR negative tumors (HR, 0.93; 95% CI 0.63-1.36; $P = .70$). Further, among patients with high polysomy or EGFR amplification, survival was significantly longer in the erlotinib treatment arm (HR, 0.44; 95% CI 0.23-0.82; $P = .008$). There was no significant survival advantage associated with the use of erlotinib in the subgroup of patients without high polysomy or EGFR amplification (HR, 0.85; 95% CI 0.48-1.51; $P = .59$).[11] These results demonstrated the feasibility of using mutation testing to guide EGFR-directed therapy in second- or third-line treatment for patients with NSCLC.

In a study published in 2009, large-scale screening of EGFR mutations in patients with advanced NSCLC was undertaken to determine its feasibility and practicality.[12] From 2005 to 2008, 2105 specimens of lung cancer from Spain were screened for EGFR mutations, and as expected, mutations were found in a low percentage of the sample population (16.6%), with a higher frequency of occurrence among women (69.7%), patients who had never smoked (66.6%), and those with adenocarcinomas (80.9%). In patients receiving erlotinib, median progression-free survival (PFS) was 14 months and median overall survival was 27 months. In this trial, male gender and the presence of an L858R mutation (compared with patients with del 19 or without the L858R mutation) predicted longer PFS.[12]

As outlined in the preceding article in this supplement, while the presence of a EGFR mutation is a predictor of treatment efficacy in NSCLC, tumor histology is also an important component for therapeutic consideration, as it helps to identify the appropriate patients for mutational testing.[2] Consequently, tissue samples should be obtained for reasons beyond just confirming the presence of malignancy and differentiating the malignancy type. Testing should begin with the planning of specimen collection. Cytologic specimens from needle biopsies can be used, but this method may not be representative of the patient's whole tissue architecture. Small volume, core needle, or endoscopically obtained forceps biopsies offer a more complete characterization of the tumor and surrounding area. Large volume tissue and paraffin blocks afford improved reliability for evaluation of the tumor

and its surrounding area. Depending on the location of the tumor itself, core needle biopsies are also a viable alternative.[13,14] The criteria for cytological sampling have been recently reviewed in detail, and recommendations for testing are summarized in the section below.[14]

Recent Recommendations on Molecular Profiling

The American Society of Clinical Oncology

The implementation of EGFR mutation testing into clinical practice has evolved rapidly in recent years. The 2011 American Society of Clinical Oncology (ASCO) provisional opinion on EGFR mutation testing recommended tumor testing for EGFR mutations in all patients with NSCLC for whom a EGFR tyrosine kinase inhibitor (TKI) is being considered as first-line therapy.[18] ASCO cited the results of the Iressa Pan-Asia Study (IPASS) that compared gefitinib and carboplatin/paclitaxel in patients with NSCLC, and found that first-line use of gefitinib resulted in longer PFS in patients with EGFR mutation (HR, 0.48; 95% CI 0.36-0.64; P <.001).[19] However, among patients who lacked the mutation, PFS was longer among those treated with carboplatin-paclitaxel (HR, 2.85; 95% CI 2.05-3.98; P <.001).[19] Overall survival in the general study population, regardless of mutation status, was similar between the 2 treatment arms.[19] These results suggest that EGFR-TKIs may be considered for certain patients with EGFR mutations, but conventional chemotherapy may be the preferred therapeutic strategy for patients without EGFR mutations.[18] Although IPASS examined the TKI gefitinib, ASCO stated that the available evidence suggests erlotinib offers a similar benefit in patients who have EGFR mutations.[18]

In an effort to produce more accurate histological classifications and mutational analyses, ASCO recommended obtaining larger samples of tissue than what has been historically collected for cytology smear preparations. Tumor enrichment by manual or laser capture microdissection may improve the results of small samples, but increases the risk of contamination and false positive tests.[18-20] However, based on currently available evidence, ASCO has only recommended mutational analysis to evaluate for EGFR mutations, as the methodology has consistently shown correlation with response to TKI therapy. The assessment of gene copy number using FISH, chromogenic in situ hybridization (CISH), and immunohistochemistry testing of EGFR have not yet established reliability. Although EGFR number based on FISH has been associated with survival, it was not recommended due to issues concerning subjectivity and its lack of predictiveness.[13,15,17,21] As shown in the **Table**,[1] mutation analysis can be performed by direct sequencing, amplification refractory mutations systems (ARMS), length analysis, and denaturing high-performance liquid chromatography. Direct sequencing is widely used and is able to detect all mutations. The most reliable predictors of response are activating mutations in EGFR exons 18 through 21, with deletions in exon 19 and single L858R point mutations in exon 21 being the most common. It should be noted that ARMS is more sensitive than direct sequencing, but detects fewer mutations. Opinions vary regarding the utility of anaplastic lymphoma kinase (ALK)-fusion gene testing in clinical practice, and it was not recommended at the time of the ASCO publication.[18,21]

The College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology

In 2013, the College of American Pathologists (CAP), International Association for the Study of Lung Cancer (IASLC), and Association for Molecular Pathology (MAP) published evidence-based recommendations regarding the use of molecular testing in patients with lung cancer to guide EGFR- and ALK-directed treatments, providing definitive guidance for when molecular testing should be performed, when a patient specimen should be tested for an EGFR mutation or ALK rearrangement, how EGFR or ALK testing should be performed, whether other genes should be routinely tested in lung adenocarcinoma, and how molecular testing should be implemented and operationalized.[22]

The CAP/IASLC/MAP guidelines recommend the use of EGFR and ALK molecular testing to select patients for EGFR-targeted TKIs in patients who have lung adenocarcinoma, regardless of histologic grade, and further suggest that patients not be excluded from testing on the basis of clinical characteristics.[22] When specimens are suboptimal and adenocarcinoma cannot be completely excluded, EGFR and ALK testing may be considered if warranted by squamous or small cell histology or clinical characteristics. Primary or metastatic tumors are considered equally suitable for testing. When multiple, separate primary lung adenocarcinomas are present, each tumor may be tested, but multiple, different areas of a single tumor do not require additional testing. Testing EGFR and ALK is recommended to occur at the time of diagnosis for patients with advanced, stage IV disease, but is also encouraged for stage I, II, or III disease. Available tissue should be prioritized for EGFR and ALK testing, and pathologists should use formalin-fixed, paraffin-embedded specimens or fresh, frozen, or alcohol-fixed specimens for PCR-based EGFR mutation testing. Cytologic samples are also suitable for EGFR and ALK testing, with cell blocks preferred over smear prepa-

Table. Summary of Common Oncogenic Driver Mutations, Their Corresponding Testing Methods, and Their Respective Inhibitors[1]

Target	Detection Method	Inhibitor
EGFR	Direct sequencing	Gefitinib, erlotinib
	Real-time polymerase chain reaction (PCR)	BIBW2992 (afatinib)
	Single-strand conformational polymorphism	PF00299804 (dacomitinib)
	High-resolution melting amplicon analysis	HKI-272 (neratinib)
		BPI-2009 (icotinib)
		EKB-569 (pelitinib)
		CI-1033 (canertinib)
		GW572016 (lapatinib)
KRAS	Direct sequencing	Not available
	Real-time PCR	
	Amplification refractory mutation system (ARMS)	
	Restriction fragment length polymorphism (RFLP)	
	Coamplification at lower denaturation temperature-PCR (COLD-PCR)	
ALK fusion	Fluorescence in situ hybridization (FISH)	PF-02341066 (crizotinib)
	Immunohistochemistry (IHC)	CH5424802 (AF802)
	Real-time reverse transcription-PCR	
MET	Quantitative PCR	PF-02341066 (crizotinib)
	Fluorescence in situ hybridization (FISH)	ARQ197 (tivantinib)
	PCR-based sequencing	GSK1363089 (foretinib)
		XL184 (cabozantinib)
		PF-04217903
		SGX523

ALK indicates anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; KRAS, V-Ki-ras2 Kirsten rat sarcoma oncogene homolog; MET, met proto-oncogene.
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rations. Each laboratory should determine the minimum proportion of cancer cells needed for mutation testing during validation. Pathologists should determine the adequacy of the specimen for EGFR testing by assessing cancer cell content and DNA quantity and quality, and by performing microdissection for tumor enrichment, as needed. Once an adequate specimen is obtained, laboratories may use any validated testing method with sufficient performance characteristics. Methods that can detect mutations with at least 50% cancer cell content are recommended, although the ability to detect mutations in specimens with as little as 10% cancer cell content is encouraged. Mutation tests should also be able to detect individual mutations with a frequency of at least 1% of EGFR-mutated lung adenocarcinomas. After EGFR testing, ALK testing should be prioritized over other proposed molecular markers. The results from testing should be made available to the clinicians within 2 weeks.[22]

It is important to note that total EGFR copy number analysis by FISH or CISH, or by immunohistochemistry for total EGFR, is not recommended for selection of EGFR-TKI therapy. In addition, KRAS testing is not recommended as the sole determinant of EGFR-TKI therapy. If testing is performed for EGFR-TKI resistance, such tests should detect a EGFR T790M mutation in as few as 5% of the cells.[22]

ALK testing should use an ALK FISH assay using dual-labeled break-apart probes for selecting ALK TKI therapy. ALK immunohistochemistry, if validated in the laboratory, may be considered for screening to select specimens for ALK FISH testing. According to the guidelines, a pathologist should be involved in selecting sections for ALK FISH testing, and should also participate in the interpretation of FISH slides, either by performing the test directly or by reviewing interpretations of the cytogeneticists or technologists. Reverse transcription-PCR is not recommended as an alternative to FISH for selection of ALK TKI therapy, and testing

for secondary mutations of ALK associated with acquired resistance to ALK inhibitors is not currently recommended by CAP/IASLC/MAP.[22]

It is recommended that EGFR mutation testing algorithms be implemented by the laboratory, provided the requirement for a 2-week turnaround time for results is met. The tests should be validated in the same manner as other molecular and FISH tests; laboratories should follow the same quality control and assurance procedures as used with other clinical assays, and should enroll in proficiency testing. Finally, the CAP/IASLC/MAP guidelines recommend that the pathologist's report include an interpretation of the results that can be easily understood by the reader.[22]

The National Comprehensive Cancer Network

The National Comprehensive Cancer Network's (NCCN) clinical guidelines for NSCLC were also updated in 2013, and suggest the first-line use of erlotinib when EGFR mutation is present[23]; testing procedures should follow the recommendations of the CAP/IASLC/MAP guideline.[22] The NCCN also recommends the use of erlotinib as a treatment option for second-line maintenance therapy following chemotherapy for adenocarcinoma, large cell carcinoma, or NSCLC not otherwise specified (NOS) when EGFR mutation and ALK testing are negative. Further, the 2013 update stated that erlotinib may be used as second- or third-line therapy, regardless of performance status.[23] In patients with squamous cell carcinoma, erlotinib is also available as a second- or third-line maintenance therapy. In the setting of EGFR mutation–positive adenocarcinoma, large cell carcinoma, or NSCLC NOS, erlotinib is recommended as a first-line agent if the EGFR mutation is discovered prior to chemotherapy. If the EGFR mutation is identified during chemotherapy, erlotinib may then be added to the current chemotherapeutic regimen, or the therapy may be switched to maintenance erlotinib. In the case of disease progression in patients with NSCLC, the continuation of erlotinib treatment is recommended; however, additional therapy may be added (eg, whole brain radiation therapy, local therapy, or systemic therapy).[23,24] The NCCN notes that KRAS mutation is associated with EGFR-TKI resistance. In advanced or metastatic nonsquamous disease, it is recommended that that crizotinib is utilized first-line for ALK gene rearrangements, with erlotinib used first-line when EGFR mutation in the patient is identified.[23,24]

Incorporating Molecular Profiling Into Clinical Practice

Mutational testing and molecular profiling can be incorporated into clinical practice by ordering the EGFR mutation status test as part of the typical pathology report. However, until recently, testing for EGFR mutation was not typically performed in the community setting unless specifically ordered, as the procedure may cost approximately $650 to $1000 and requires up to 2 weeks for results.[21]

One cost-effective method of delivering optimal patient care is to follow approved clinical practice guidelines and to reduce variability in practice. A retrospective study published in 2010 by Neubauer et al examined the cost-effectiveness of the Level 1 Pathways program—a physician-led initiative that promotes the use of standardized, evidence-based treatment—in 1409 patients with NSCLC who had initiated a chemotherapy regimen between July 1, 2006, and December 31, 2007, at 8 practices in the US oncology network. While the study did not demonstrate a difference in overall survival, researchers did find that patients who were treated according to Level 1 Pathways for NSCLC had 35% lower average 12-month outpatient costs ($18,042) compared with those who were not treated according to the program ($27,737).[25]

Despite the defined recommendations for EGFR mutation testing and treatment guidelines from organizations such as ASCO, CAP/IASLC/MAP, and NCCN, the use of EGFR testing remains underutilized, having been ordered by 12% of US acute care hospitals in 2010.[26] Potential reasons for this lack of adoption could be the uncertainty regarding the testing and its meaning, a lack of patient insurance coverage, and the lack of pharmacoeconomic assessments to determine the value of mutational testing and subsequent treatment. It should be noted that at the time of this publication, companion diagnostic tests, which allow clinicians to check whether patients are suitable candidates for certain targeted therapies, have been approved for use with erlotinib, afatinib, and crizotinib.

Although data remain limited, several studies have now evaluated the cost-effectiveness of EGFR-directed therapies.[27-35] In a Dutch comprehensive cost model, erlotinib was compared with docetaxel and best supportive care (BSC) in relapsed NSCLC. Docetaxel and erlotinib were assumed to have the same efficacy. Costs in 2004 Euros were €24,939 ($33,169 USD in 2004) for docetaxel, €23,436 ($31,170 USD) for erlotinib, and €15,450 ($20,549 USD) for BSC. According to the model-based analysis, life-years gained (LYG) were 0.84 for both pharmacologic treatments, and 0.62 for BSC. Erlotinib was cost-saving in most scenarios, with the incremental cost-effectiveness ratio (ICER) for erlotinib versus BSC equating to €37,551 ($49,943 USD) over a treatment duration of 4.3 months, which would be considered cost-effective at a willingness to pay (WTP) set at €50,000 ($66,500 USD).[27]

Other studies have also found the TKIs erlotinib or gefitinib to be cost-effective as second- or third-line agents, or as postchemotherapy maintenance therapy. In those analyses, the costs of erlotinib were generally lower than conventional chemotherapy due to lower administration cost, reduced adverse events, and decreased acquisition costs, despite similar efficacy.[28-31] Another study evaluated alternative testing methods, including EGFR protein expression and EGFR gene copy number, in patients about to undergo second-line therapy.[32] The study did not confirm the cost-effectiveness of these alternate testing methods, demonstrating ICERs of $162,018 (in 2006 USD) per quality-adjusted life-year (QALY) for providing erlotinib with EGFR gene copy testing compared with providing erlotinib without testing. Further, the strategy of assessing protein expression demonstrated a comparative ICER of $179,612 (in 2006 USD) per QALY.[32] This study supported the current strategy of adding erlotinib for second- or third-line use without EGFR testing.[19-24]

Studies have also evaluated the use of targeted therapy with EGFR testing to guide first-line therapy.[33-35] A decision analytic model examined EGFR testing and first-line gefitinib followed by conventional chemotherapy for patients harboring activating mutations compared with standard care with first-line chemotherapy and second-line gefitinib.[32] For conventional chemotherapy followed by second-line gefitinib with no EGFR testing, the cost in 2010 Singaporean dollars was $47,100 ($36,738 USD in 2010) for 0.87 QALY. EGFR testing followed by first-line gefitinib for EGFR mutations and second-line chemotherapy cost approximately $44,700 ($34,866 USD) for 0.91 QALY. The incremental cost savings associated with EGFR testing-guided therapy was $2400 ($1872 USD) and the incremental ICER was 0.04, providing evidence that this strategy is cost-effective.[33]

The potential benefits of this strategy were also noted by the authors of another study that used an analytic model to evaluate platinum-based combination chemotherapy compared with targeted therapy. Patients in the platinum-based chemotherapy group received 1 of 3 standard regimens: carboplatin and paclitaxel; carboplatin and pemetrexed; or carboplatin, pemetrexed, and bevacizumab. In the targeted therapy group, patients with EGFR mutation-positive tumors received erlotinib; in this group, 2 scenarios were evaluated: (1) testing only when an adequate tissue sample was available, and (2) testing when a repeat biopsy was necessary for adequate tissue.[34] The study was conducted in a theoretical group of patients with stage IV or recurrent adenocarcinoma of the lung. Costs were examined in 2010 US dollars. Based on the model, testing an existing specimen for EGFR and treating with erlotinib yielded an ICER of $110,644 USD per QALY when compared with first-line therapy with carboplatin-paclitaxel, and an ICER of $122,219 compared with the rebiopsy strategy. If a WTP limit of $100,000 per QALY was set, then testing for EGFR mutations was cost-effective 58% of the time, and rebiopsy was cost-effective 54% of the time. Further, compared with carboplatin, pemetrexed, and bevacizumab, the ICER for the testing an existing sample scenario was $25,547 per QALY and the ICER for the rebiopsy scenario was $44,036 per QALY.[34]

Summary

For patients with NSCLC, and especially those affected by advanced disease, biomarkers are an increasingly influential component in today's therapeutic landscape, providing the opportunity to guide effective, targeted treatments for patients who may benefit the most. Prominent organizations, such as ASCO, CAP/IASLC/MAP, and NCCN, have developed clinical guidelines and evidence-based recommendations for the analysis and appropriate use of biomarkers and molecular testing in an effort to improve treatment efficacy and patient outcomes while reducing healthcare costs and inappropriate utilization. According to those recommendations, testing in a patient with NSCLC should be initiated with an adequate and thorough histologic evaluation to differentiate the subtypes of lung cancer, and to determine the presence or absence of other predictive indicators, such as EGFR mutations and ALK fusion genes. Whenever possible, these evaluations should be performed prior to initiation of therapy, as evidence has demonstrated the cost-effectiveness of this strategy.[18,22] Operating in a cost-constrained healthcare environment, it is important to obtain an adequate initial sample to reduce patient discomfort, increase convenience, and maintain the cost-effectiveness of the targeted treatment strategy.[34] Research has repeatedly shown that targeted therapies in response to the presence of EGFR mutation in patients with NSCLC presents a cost-effective approach to conventional first-line treatments. With ongoing research and further data collection in the clinical space for NSCLC, treatment paradigms are shifting, and an increasing number of clinicians, healthcare providers, and managed care authorities are realizing the cost-effectiveness, value, and potency of personalized, targeted treatment strategies.

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