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Effective Use of Biomarkers in the Identification of Targeted Therapies in Patients with Non-Small Cell Lung Cancer

White Paper

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Contents

Introduction

Improving care for non-small cell lung cancer (NSCLC) patients is important because NSCLC accounts for 81% of lung cancer cases. There are three main subtypes of NSCLC: squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. The subtypes have varied characteristics. For example, adenocarcinoma is slightly more common in women, squamous cell carcinoma is more aggressive than adenocarcinoma, and large cell carcinoma is more aggressive than the other two NSCLC subtypes. In 2017-2018, the two-year relative survival rate for NSCLC was 54% in women and 43% for men, with the five-year survival rates being higher in women at all diagnosis stages. These rates may be due to differences in tumor characteristics and hormonal influence on treatment response. Women are also more likely to have tumors with genetic mutations, such as in the EGFR gene, that are responsive to targeted therapies.[1,2]

Nearly two-thirds of patients with NSCLC have an oncogenic driver mutation, and more than 50% of these mutations are clinically actionable.[3-8] Currently, there are more than 20 FDA-approved treatments that target oncogenic drivers in NSCLC to help guide treatment decisions.[5,9-12] Targeted treatment has subsequently improved overall five-year survival rates in patients with metastatic NSCLC.[5,13]

Biomarker testing is required to identify appropriate targeted therapies to customize treatment. Recommended biomarker testing for NSCLC includes EGFR, KRAS, ALK, ROS1, BRAF, RET, MET, NTRK1/2/3, ERBB2 (HER2), and PD-L1.[5,10,14] Yet the MYLUNG Study demonstrated that only 46% of patients receive testing for at least five NSCLC-associated biomarkers.[15] Challenges of tissue acquisition include invasiveness, limited/exhausted tissue, potential sampling bias due to intratumoral heterogeneity, cost, inability to sample all metastatic sites, and variable/limited accessibility of tumor sites. Communication also poses barriers due to the necessity of involving multiple care team members and delays in testing and treatment.[5,16-24]

As useful and effective as biomarker testing and targeted treatment are for patients with NSCLC, many health systems have had to change existing workflows and implement new procedures to incorporate specific genomic testing for tumor types to treat oncologic disease. Healthcare providers find it increasingly difficult to determine specific therapies and interventions for patients without these test results. Therefore, more research is needed to develop a new framework in which best practices in biomarker testing can be used to improve clinical practice in NSCLC.

Methods

Premier's PINC AI™ Applied Sciences (PAS) conducted a technical expert panel meeting with healthcare providers, administrators, and key stakeholders from across the US to gain a better understanding of how health systems of all types and sizes (e.g., academic, community) use biomarker testing in therapeutic decision-making for patients with NSCLC at and after first-line therapy.

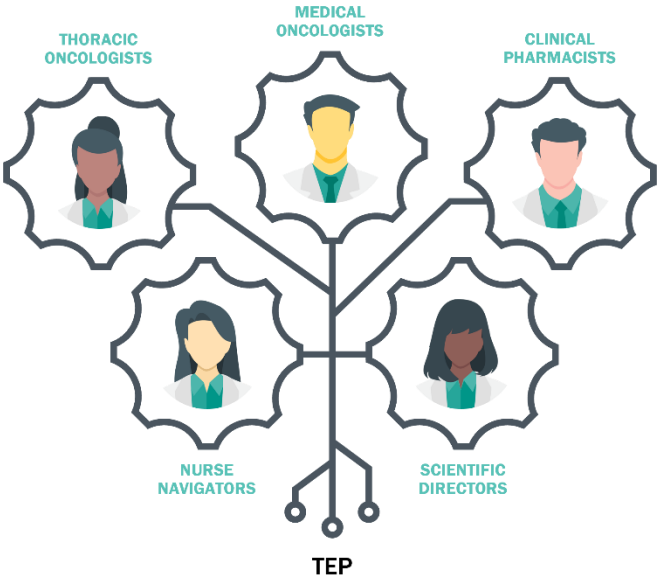
The objectives of the meeting were to:

- Explore processes and protocols for identifying and treating patients with biomarker-positive NSCLC
- Discuss issues surrounding genomic testing: timing, delivery of results, documentation of results, utility in determining treatment

- Develop an understanding of what works well and potential areas of improvement
- Develop a resource for instituting best practices for identification, testing, documentation, and treatment of patients with biomarker-specific mutations and NSCLC
- Document existing information on clinical perspectives, processes/workflows, and practices for NSCLC care management

PINC AI developed an agenda and discussion guide to explore questions about the use of biomarker testing in the NSCLC patient population. Further, PINC AI recruited panel Advisors with expertise in precision medicine and care pathways for the treatment of patients with NSCLC that includes biomarker testing. The Advisors comprised thoracic and medical oncologists, clinical pharmacists, a nurse navigator, a scientific director, and represented academic, hybrid, and community hospitals, as well as independent delivery networks from both coasts and the central US.

This paper outlines findings about knowledge, attitudes, and beliefs of the above-mentioned stakeholders concerning the challenges of implementing biomarker testing in NSCLC and barriers to/facilitators of adoption of workflows and standardizations and decision-making protocols for specific treatments or patient cases. All information presented here represents the opinions of the Advisors, and it does not necessarily represent the viewpoints of PINC AI or the sponsor.



Findings

Current State of Biomarker Testing

Both academic and community hospitals face operational and logistical challenges in obtaining biomarker testing in a timely manner. In addition, oncologists vary in how they interpret the National Comprehensive Cancer Network (NCCN) guidelines, which are the primary guidelines used to treat patients with NSCLC. The Advisors stated that this issue is largely due to the autonomy and discretion oncologists have in how they interpret and apply the guidelines, what diagnostic tests they use, and how they use both in decision-making for treatment. One Advisor added that the NCCN guidelines do not completely account for the complexity of data readouts from sequencing.

One difference noted between institution types is that many academic institutions have in-house laboratory and pathology services that can provide more timely testing. Community hospitals, on the other hand, often depend on outsourced testing services and have other resource constraints in their pathology departments. One Advisor noted that, *"it is challenging to institute best practices because we have a wide range of hospital systems across the tri-state area. Some are more community practices, and the flow of patients is very complicated in some places. There are some operational and logistical challenges in getting biomarker testing in a timely manner."*

Further, the site of care is a challenge for community hospitals because initiating biomarker testing occurs in the outpatient setting. This means that patients who are diagnosed with NSCLC in a hospital must wait to obtain biomarker testing until after they are discharged. One Advisor described it this way: *"Most patients are sick in the hospital when we see them. We do a biopsy and must send the tissue for NGS and then do a liquid biopsy. Because we do all that, we cannot just proceed when the patient is in the hospital. We must wait until the patient is healthy enough to be an outpatient, even if we have a biopsy tissue, to run anything. We know the patient could be there for five days, a week, or longer if they have a biopsy and chest tube complication. We know we will do something for them in the outpatient setting, but we must wait until the patient is seen in the office to initiate running an NGS. We are killing time knowing we want to do something — but we can't."*

For these patients as well as for new patients seen in the outpatient setting who have testing initiated, the average turnaround for tissue testing often exceeds three weeks, and liquid biopsies take about five days.

Finally, tracking the oncology practice's testing results was highlighted as challenging due to limited staffing resources and because there are no standard testing pathways or algorithms currently used. Advisors agreed that health systems want greater standardization in the testing process – from ordering to sample acquisition and reporting.

Figure 1: Current biomarker testing rates among Advisor-represented sites

TESTING PRACTICES AND VENDORS REPORTED FROM ADVISORS
Tempus, Guardant, Caris, Signatera
CGP for all NSCLC patients; PDL1 for all late-stage NSCLC; single gene testing for BRAF, EGFR; Tempus and GeneDx for NGS; FoundationOne for ctDNA
PDL1 in-house; Reflexively outsource tissue and liquid biopsy; Tempus
Predominantly outsource testing; just purchased NGS equipment
Predominantly outsource tissue and liquid biopsies at the time of diagnosis; Caris is used for tissue biopsies; FoundationOne is used for liquid biopsies
Predominantly outsource testing; NGS and liquid biopsy; Caris, FoundationOne, Guardant, Tempus
Predominantly in-house testing; reflex testing for EGFR, ALK; PDL1 for the majority of patients; liquid biopsy/ctDNA for all patients; Guardant for ctDNA

Operational Considerations

Advisors reported that the process of identifying and testing patients, creating and maintaining documentation, and interpreting and communicating test results is "complicated" and "clumsy" across health systems.

Documentation

In particular, the electronic health record (EHR) is viewed as a major pain point because many current systems are not designed to manage the breadth and depth of biomarker testing reports efficiently or to meet the providers' need for accessibility. Various Advisors noted challenges accessing test reports across various platforms as well as a lack of consistency in where reports are stored. One Advisor emphasized, *"This has been such a problem. There has not been a good place for them [the test reports] to live within Epic."* Another noted that Epic *"is very provider-specific. It is a clumsy process, prone to errors if I am not on top of each step…if I do not explicitly indicate that it needs to be scanned into the patient's chart, it will not be in the chart. That is not a good system, but that is how it is right now."*

Two other Advisors use OncoEMR®. One said, *"One of the difficulties is that we do not have a good place in the OncoEMR. One, it is a 50–100-page scanned report; two, there is no good spot for it. Our physicians order all testing, and they are sent to different outside vendors. We have purchased NGS equipment and hope to offer NGS testing on-site by the end of the year."* The other Advisor agreed, and added, *"It is hard for us to get the test results. We have to keep looking for them after the MAs scan them."*

Figure 2 shows the different ways Advisors described their documentation processes.

Figure 2. Site processes for biomarker testing ordering, documenting, and receiving results

EXAMPLE 1	• Nurse navigator scans requisition form into "Notes" section of "Chart Review." • Results scanned into "Media Tab." • Dates documented on "Snapshot." • Relevant documents, e.g., tests, path reports, imaging reports, and progress notes, are "bookmarked" together.
EXAMPLE 2	• Reports are emailed directly from third-party vendors. • Oncologist logs into secure vendor portal. • Downloads report. • Shares report with oncology team member, MAs, or "liaisons" who upload reports into "Media" tab.
EXAMPLE 3	• Oncologist gives nurse navigators access to vendor portals. • Navigator downloads reports. • MAs scan reports into Epic. • Some MAs name and store reports under "Media;" others put it elsewhere.
EXAMPLE 4	• MA scans results into EHR. • Reports are usually put in "Pathology" folder. • Sometimes reports are put in "Lab" or "Miscellaneous" folders.

One Advisor noted some positive aspects of their system, which is relatively uncomplicated for accessing reports because most testing occurs in-house. Specifically, this Advisor said that testing reports are in the "Results" tab, which has "Pathology," "Imaging," and "Molecular" tabs for file storage. With in-house testing and the resulting integration of documentation with the EHR, the Advisor said turnaround time for reporting results may be reduced.

There are also operational issues with biomarkers that are actionable following first-line therapies. One Advisor stated they cannot test without prior authorization, which causes significant time delays in initiating second-line therapies. Tracking the HER2 and KRAS G12C results is also a highly manual and burdensome process, as is the process for molecular testing documentation management. Another pointed out that they do not have nurse navigator support. Therefore, the day a molecular testing report is received, any relevant alterations in the progress note must be entered manually. One Advisor described a method of bolding progress notes if there is a KRAS G12C, so that it is obvious the patient has a targetable mutation in the second line, and it serves as a reminder of a clinical pathway that can be followed.

Molecular Tumor Boards

Tumor boards serve various purposes in health systems. They are a general oncology consult service, a diagnostic forum for complex cases, and an educational platform to introduce new data and innovation. Six Advisors indicated that they have tumor boards at their sites, one of which also used a virtual tumor board. One Advisor indicated they use multidisciplinary committees instead of tumor boards, and one Advisor did not respond to this question.

Two Advisors described their systems' tumor boards. One said that their molecular tumor board comprises an interdisciplinary team that discusses cases. Levels of evidence are referenced, recommendations are made, and letters are written to treating physicians indicating information such as "drug X for mutation Y." The nurse navigator communicates the board's results to the treating physician. This Advisor noted that selecting and conducting testing is at the treating physician's discretion, and the physician and patient collaborate on treatment decisions.

Another Advisor described their sequencing tumor board as a team that includes a pharmacist, a computational scientist, a pathologist, and a genetic counselor. This board is reserved for complex cases and convenes before meeting with the treating physician to discuss the patient case, review data (including RNA sequencing data and clinical trials), and review guidelines and available targeted therapies for specific mutations. When they meet with the treating physician, they then provide a recommendation. The Advisor added that this forum also serves as an educational forum, and that *"the oncologists rely upon the expertise of the board to take some of the burden off their plate."*

Advisors stated that there is some sensitivity concerning the role of tumor boards for complex cases and the subsequent recommendations that treating physicians can use. Depending on the organization, sensitivities may include the uncertainty of the recommendations, the autonomy of the treating physician, and/or the legal implications. One Advisor stated, *"… you cannot have a dynamic recommendation if you are talking about a rare mutation, such as an EGFR mutation. You cannot have Level 1 evidence of anything, so there are some implications for how you make those tumor board recommendations objectively. It cannot really be a consult service; you cannot have a consult with Recommendation A or Recommendation B."*

Communicating Test Results

While it is important to make sure a patient's biomarker test results are known and carried through in the clinical decision-making process, the Advisors described challenges involving heavy reliance on manual processes and personal reminders that highlight the need for better automation, streamlined workflow, and effective information systems. One said, *"It's a very manual process. A lot of talking to people in the hallway and having more and more people attend our molecular tumor board; sending the nurse navigator to the actual tumor board so when decisions are being made, she can weigh in and say, 'Remember.'"* Other Advisors echoed this, with one adding that it is a *"convoluted process, mostly done manually, checking in-boxes, checking patients' charts, remembering, and reminding each other."* Another stated that in a complex system with operational issues and poor communication, there will be a potentially negative effect on patients - *"How do we make sure that when patients are flagged for an EGFR mutation, or whatever, they are getting appropriate treatment? If you leave it up to the oncologist, there is always going to be a certain percentage of patients not getting adequate treatment."*

There is also variability and disparity in patient access to their biomarker results. Access is dependent on the system the healthcare provider uses. This can lead to significant inconsistencies in patient experiences and potentially influence their understanding of their diagnosis and treatment plans. Several Advisors reported that for health systems that use Epic, biomarker test reports are automatically uploaded into the "MyChart" patient portal. However, providers think the biomarker reports are too complex and confusing for patients. Other health systems discuss test results with patients rather than providing them with a report.

Oncology-Pathology Partnership

One Advisor described their site's proactive efforts to meet some of the challenges discussed in the meeting, including bringing as much testing in-house as possible and moving ownership of testing to the laboratory/pathology department to improve tissue stewardship, turnaround times, tracking, documentation, and reporting. The overall goal is to develop and promote an algorithm-based testing institution pathway that supports clinical decision-making in NSCLC. While the system will initially still send their tumor profiling to outside laboratories, that process is expected to be brought in-house for the next iteration of the model. This model could potentially streamline processes, increase efficiency, and ensure greater quality control.

The in-house model being pilot tested at this health system is based on NCCN and other guidelines for NSCLC, and it was developed in collaboration with oncologists, laboratory staff, and pathology leadership. In the proposed workflow, pathology will initiate NSCLC biomarker testing based on the established pathway. The results will be interpreted and embedded in the EHR before the oncologist sees the diagnosis and a patient visit is scheduled.

A key challenge in developing this program was that oncologists wanted to control the process and decide what tests to order. To address this challenge, the pathology department collaborated with a lung cancer physician advisory board to develop the pilot program as well as education on its components and the time needed for pilot testing as well as the potential time saved in the ordering, obtaining, testing, and resulting process.

The Advisor summed up the program, stating that *"An in-house lab that controls all of that and is a steward of the tissue can have significant benefits… We are trying in-house testing at our health system to enable significant clinical utility and developing guidelines to remove some of those barriers. We are working closely with our oncologists to take ordering out of their hands and potentially put it in the pathologists' hands where there is a concrete algorithm for the late-stage NSCLC patient so they can get these series of tests before the oncologist even sees them in the clinic. So, when the patient returns after the biopsy, they have their results and can put together a plan. They can have their autonomy; some follow NCCN guidelines, and some follow their own practice. We are looking to provide institutional guidelines for handling those cases and trying to speed it up for some of the patients with the oncologists after the biopsy when the results are ready."*

While highlighting the benefits of an in-house lab, there is also a need to understand the potential roadblocks to implementing this model more broadly across other health systems and what measures are being taken to navigate these barriers. For example, the model's cost effectiveness is questionable and may pose financial challenges, and the expertise and tools necessary may not be available for smaller oncology practices.

Nurse Navigators

Nurse navigators have an increasingly important role in managing biomarker testing for NSCLC and in addressing the many challenges oncologists and patients face. One Advisor said, *"Everything…is getting more complex. Finding a way to encapsulate this information so that it is more standardized and useful, and quicker for the patient — we are absolutely on board with that. But it is a beast of a problem."*

Nurse navigator roles and responsibilities can vary by health system. Advisors noted that this role may focus on testing, supporting an entire cancer institute, specific oncology practices, or individual oncologists. In other systems, they may be dedicated to clinical care and have no testing responsibilities. One Advisor added that the role does not exist in community hospitals, which increases the burden of biomarker testing management for community providers. Other Advisors agreed, stating that organizations that do not have this role rely on registered nurses (RN) and medical assistants (MA) for these responsibilities. Another Advisor added that their nurse navigators are training clinic support staff, the RNs and MAs, to manage the biomarker testing so that they can focus on new patients and broader care coordination.

One Advisor provided an example of how nurse navigators were introduced into their health system and the effect it has had. *"I tried hard to get reflex testing in place and was unable to do so. So, I hired a nurse navigator to navigate the next-generation sequencing testing. When she started, we went to the groups and said, 'You know you can order any test you want; we want to order the test you want, so can we come to a consensus?' The lung and ovarian groups came to a consensus almost immediately about what test they wanted to order and what stage, so we wrote that down and made it a process for those groups. [When] we evaluated our nurse navigator, the introduction of [that role] reduced the turnaround time from about six weeks, counting from the time of diagnosis to the time of results, to about two and a half weeks. A week of that was within pathology."*

Treatment Decisions

Use of Guidelines

Treatment patterns show a failure to follow appropriate evidence-based pathways.[23] Advisors view this state of clinical practice as a major problem because many patients are not getting potentially beneficial therapies.

Use of Artificial Intelligence

The Advisors thought artificial intelligence (AI)-based innovations could provide potential solutions to address oncology needs such as:

- More scalable solutions for getting tumor board-like expertise to community oncology practices across a broad geographical footprint
- Additional support with clinical decision-making
- Better medical records management to include query functionality and summary notes capabilities
- Alerts on new drugs, new trial data, and guideline updates and the ability to match this information with the patient's status and disease progression to inform treatment plans

While the Advisors shared interest in AI possibilities, only two Advisors indicated they were conducting pilot studies on AI use. One is looking at using AI to support medical records management and provide the capability to pull specific data. Another is focusing on using AI to predict outcomes, and instead of using tumor boards, it would use AI to make recommendations. Specifically, the Advisor stated that algorithms were being developed *"based on a molecular tumor board database that has 3,000 recommendations in it. So, with all this clinical data, and the particular genetic recommendations, and what we recommended, and how the patients did, the question is, can the machine learn from that and make recommendations for other patients? The first step is to show that it makes the same recommendations because that is the data that it was trained on. We have to make sure it makes the same recommendations we would have made, and the next step after that is to see if it can make better recommendations."*

Best Practices

Advisors had some suggestions for best practices to support biomarker testing in NSCLC. These included:

- Using guideline- and pathology-driven testing and standardizing in-house testing.
- Establishing and adhering to tissue stewardship practices.

STAYING CURRENT ON NEW TREATMENTS

Participants indicated a variety of ways they stay current on the most recent data and guidelines for NSCLC

- Conferences (ASCO, JCO AACR, World Lung, etc.)
- Discussions
- Education materials from industry
- Email bulletins from the Heme-Onc Pharmacists Association
- Journal articles
- Key Opinion Leader (KOL) discussions
- Medical science liaisons
- NCCN updates
- Tumor boards
- Virtual meetings
- White papers

- Establishing molecular tumor boards as a specific tumor board to inform decision-making and protocols for molecular testing. Within the boards, having a core of molecular, research, and medical expertise.
- Training and using nurse navigators to take ownership of molecular testing process and to provide support for providers and patients in person and virtually. Further, nurse navigators could also support patient engagement in clinical trials — particularly for the underserved.
- Embedding "best practice alerts" in the EHR. Examples include alerts for patients who may be appropriate for a particular treatment at the time of progression on first-line chemotherapy/immune-oncology, alerts that indicate lack of biomarker testing in a patient's file; alerts for relevant biomarkers for second-line treatments, such as KRAS G12C.
- Performing quality control of test turnaround times for in-house testing.

Figure 3 summarizes various best-practice approaches to addressing biomarker testing in the NSCLC patient population.

Figure 3. Best practice approaches for challenges and gaps in biomarker testing in NSCLC

KEY CHALLENGES / GAPS	APPROACHES
Physician autonomy	• Engage oncologists in collaborative decision-making to support best practices • Use tumor boards as a platform for education and consultation
Knowledge gaps	• Use expertise of molecular tumor board members
Variability in testing and testing stewardship	• Bring testing in-house • Develop guideline- and pathology-driven protocols • Simplify and standardize pre-analytical molecular phase of diagnostic workup • Hire nurse navigators to own these responsibilities
Variability in records management and complexity of tracking test results	• Hire nurse navigators to own these responsibilities • Use "bookmarker" features in EHRs to consolidate location of test results • Have test vendors eFax reports with documents that can be uploaded • Standardize oncology notes to include molecular testing results
Access to pathologists	• Use virtual tumor boards, when possible and appropriate • Access test vendors' professional resources for results interpretation
Staffing constraints	• Teach clinic RNs and MAs responsibilities for biomarker testing typically owned by nurse navigators • Hire a molecular testing navigator who partners with pathology and oncology teams
SDoH and the underserved patient population	• Access industry funding to provide patient navigators to support comprehensive biomarker testing programs for the underserved
Current payment models	• Champion patient assistance programs and seek legislative support requiring insurance companies to pay for biomarker testing

Conclusions

Health systems across the US have varied experiences with the current complex systems and operational issues that affect biomarker testing for patients with NSCLC. There are many challenges in ensuring patients' biomarker test results are known and carried through in the clinical decision-making process, both among care teams and with patients. As the Advisors have noted, treatment patterns do not necessarily reflect evidence-based guidelines, regardless of geography or institution type. Academic and community hospitals both face knowledge gaps on oncology guidelines, diagnostics, and treatments. They also encounter significant operational and logistical variability in testing and its accompanying stewardship, medical records management, access to pathologists and other staff, and payer prior authorizations and restrictions on access to testing.

Biomarker testing, documentation, interpretation, and communication all present problems and complications across health systems. The EHR is a particular pain point in oncology care because systems cannot manage the processes needed to order, track, and extricate biomarker testing reports efficiently nor to meet providers' need for accessibility to data. Indeed, many processes are highly manual and burdensome. Current testing pathways also exhibit variability and delays, which results in long turnaround times due to operational issues, prior authorization, costs, and the inability to perform targeted biomarker testing in the inpatient setting.

Nurse navigators are taking a greater role in managing biomarker testing, reporting, and communication. However, their roles and responsibilities vary across health systems, and the role does not exist in community hospitals, which must rely on other sources for biomarker testing management.

Tumor boards are available at most academic institutions, and some even have specific molecular tumor boards. Community hospitals, however, may not have this resource and again must rely on other resources, such as multidisciplinary committees, to aid in treatment decision-making.

AI-based innovations may provide potential solutions to some of these problems, such as easier access to clinical and diagnostic expertise and improved medical records management.

PAS is making this paper available on its PINC AI Platform for health systems across the country.

Limitations

Although forum participants broadly represented stakeholders making decisions about biomarker testing, there were no patient or payer representatives. In addition, only NSCLC was discussed in the context of biomarker testing, which may not reflect the challenges, resources, and other considerations that other cancers and conditions may face with this method of testing. These perspectives may merit further research.

References

1. American Cancer Society. *Cancer Facts & Figures 2023*. 2023. Accessed May 4, 2023. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2023/2023-cancer-facts-and-figures.pdf
2. Ganti AK, Klein AB, Cotarla I, Seal B, Chou E. Update of Incidence, Prevalence, Survival, and Initial Treatment in Patients With Non-Small Cell Lung Cancer in the US. *JAMA Oncol*. Dec 1 2021;7(12):1824-1832. doi:10.1001/jamaoncol.2021.4932
3. Chevallier M, Borgeaud M, Addeo A, Friedlaender A. Oncogenic driver mutations in non-small cell lung cancer: Past, present and future. *World J Clin Oncol*. Apr 24 2021;12(4):217-237. doi:10.5306/wjco.v12.i4.217
4. Jordan EJ, Kim HR, Arcila ME, et al. Prospective Comprehensive Molecular Characterization of Lung Adenocarcinomas for Efficient Patient Matching to Approved and Emerging Therapies. *Cancer Discov*. Jun 2017;7(6):596-609. doi:10.1158/2159-8290.CD-16-1337
5. Oncology Specialty Group. *Best practices along the tissue journey in NSCLC*. 2022. https://www.onclive.com/view/best-practices-along-the-tissue-journey-in-nsclc
6. Rotow J, Bivona TG. Understanding and targeting resistance mechanisms in NSCLC. *Nat Rev Cancer*. Oct 25 2017;17(11):637-658. doi:10.1038/nrc.2017.84
7. Russo A, Franchina T, Ricciardi GR, et al. A decade of EGFR inhibition in EGFR-mutated non small cell lung cancer (NSCLC): Old successes and future perspectives. *Oncotarget*. Sep 29 2015;6(29):26814-25. doi:10.18632/oncotarget.4254
8. Vu P, Patel SP. Non-small cell lung cancer targetable mutations: present and f. *Precis Cancer Med*. 2020;3(5)
9. Adib E, Nassar AH, Abou Alaiwi S, et al. Variation in targetable genomic alterations in non-small cell lung cancer by genetic ancestry, sex, smoking history, and histology. *Genome Med*. Apr 15 2022;14(1):39. doi:10.1186/s13073-022-01041-x
10. Majeed U, Manochakian R, Zhao Y, Lou Y. Targeted therapy in advanced non-small cell lung cancer: current advances and future trends. *J Hematol Oncol*. Jul 8 2021;14(1):108. doi:10.1186/s13045-021-01121-2
11. National Cancer Institute. Targeted therapy approved for lung cancer. Accessed May 4, 2023. https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/approved-drug-list#targeted-therapy-approved-for-lung-cancer
12. VanderLaan PA, Rangachari D, Costa DB. The rapidly evolving landscape of biomarker testing in non-small cell lung cancer. *Cancer Cytopathol*. Mar 2021;129(3):179-181. doi:10.1002/cncy.22334
13. Mileham KF, Schenkel C, Bruinooge SS, et al. Defining comprehensive biomarker-related testing and treatment practices for advanced non-small-cell lung cancer: Results of a survey of U.S. oncologists. *Cancer Med*. Jan 2022;11(2):530-538. doi:10.1002/cam4.4459
14. Aisner DL, Riely GJ. Non-small cell lung cancer recommendations for biomarker testing and treatment. *J Natl Compr Canc Netw*. 2021;19(5.5):610-613. doi:10.6004/jnccn.2021.5020
15. Robert NJ, Espirito JL, Chen L, et al. Biomarker testing and tissue journey among patients with metastatic non-small cell lung cancer receiving first-line therapy in The US Oncology Network. *Lung Cancer*. Apr 2022;166:197-204. doi:10.1016/j.lungcan.2022.03.004
16. Arnaud A. Costs and outcomes comparison of tissue and blood based biopsies for the purpose of biomarker testing. *Value Health*. 2016;19(3):PA143-A144.
17. Bidard FC, Weigelt B, Reis-Filho JS. Going with the flow: from circulating tumor cells to DNA. *Sci Transl Med*. Oct 16 2013;5(207):207ps14. doi:10.1126/scitranslmed.3006305

18. Francis G, Stein S. Circulating Cell-Free Tumour DNA in the Management of Cancer. *Int J Mol Sci*. Jun 19 2015;16(6):14122-42. doi:10.3390/ijms160614122
19. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med*. Mar 8 2012;366(10):883-892. doi:10.1056/NEJMoa1113205
20. Lin L, Lin DC. Biological Significance of Tumor Heterogeneity in Esophageal Squamous Cell Carcinoma. *Cancers (Basel)*. Aug 12 2019;11(8)doi:10.3390/cancers11081156
21. Perakis S, Speicher MR. Emerging concepts in liquid biopsies. *BMC Med*. Apr 6 2017;15(1):75. doi:10.1186/s12916-017-0840-6
22. Remon J, Caramella C, Jovelet C, et al. Osimertinib benefit in EGFR-mutant NSCLC patients with T790M-mutation detected by circulating tumour DNA. *Ann Oncol*. Apr 1 2017;28(4):784-790. doi:10.1093/annonc/mdx017
23. West HJ, Lovly CM. Ferrying Oncologists Across the Chasm of Interpreting Biomarker Testing Reports: Systematic Support Needed to Improve Care and Decrease Disparities. *JCO Oncol Pract*. Mar 28 2023:OP2300010. doi:10.1200/OP.23.00010
24. Zarinshenas R, Amini A, Mambetsariev I, et al. Assessment of Barriers and Challenges to Screening, Diagnosis, and Biomarker Testing in Early-Stage Lung Cancer. *Cancers (Basel)*. Mar 3 2023;15(5)doi:10.3390/cancers15051595

