

Updates Regarding Biomarker Testing for Non-Small Cell Lung Cancer: Considerations from the National Lung Cancer Roundtable



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Introduction

Lung cancer is the most common cause of cancer-related deaths worldwide, with 1.7 million deaths per year.¹ The cancer of most patients is diagnosed at the stage of locally advanced/metastatic disease. For the past several decades, therapies have offered limited potential for cure or significant prolongation of life. Historically, treatment of patients with advanced or metastatic NSCLC focused on histological diagnosis, assessment of age, comorbidities, and performance status and centered on doublet chemotherapy. No specific biomarkers were required to initiate therapy.

We are in a period of rapid change in the assessment and treatment of patients with NSCLC. Numerous trials have led to approval of therapies with corresponding biomarker diagnostics. With so many new treatment options, biomarker testing at diagnosis is important to determine the best options.

As a result of these successful trials, multiple evidence-based options utilizing targeted treatments and immunotherapies have been published in guidelines by major professional organizations (e.g., the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology [CAP/IASLC/AMP], American Society of Clinical Oncology [ASCO], European Society of Medical Oncology, and the National Comprehensive Cancer Network).²⁻⁷ Recommended genes for testing currently include

EGFR, ALK receptor tyrosine kinase gene (*ALK*), *ROS1*, and *BRAF*.

Despite these authoritative recommendations, some patients with advanced or metastatic NSCLC do not undergo biomarker testing at all or are not assessed for all recommended biomarkers. In a 2016 retrospective review of claims submitted by 2623 patients with metastatic NSCLC, MacLean et al.⁸ reported that 61% of patients received biomarker testing at any time in their claims history. Among those treated with

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chemotherapy or targeted therapies, 89% received biomarker testing before treatment initiation. Biomarker testing was defined as any Common Procedure Terminology code indicative of fluorescence in situ hybridization, polymerase chain reaction, or other molecular genetic tests.⁸ A 2018 paper published jointly by the Friends of Cancer Research and Deerfield Institute reported results from an online market research survey of 157 oncologists.⁹ Across institutions, 87% of patients with stage IV lung adenocarcinoma received either single-gene or multigene testing. The testing rate was higher at academic medical centers (96%) than at community centers and private clinics (84% and 81%, respectively). More than half (58%) of the oncologists reported using single-gene assays. A significant difference in the rate of multigene panel testing by institution type was observed (59%, 33%, and 28% by academic, private, and community institutions, respectively [$p = .02$]). For genes with associated targeted therapies, the rate of testing for *EGFR* was the highest (72%), followed by the rates of testing for *ALK* and *ROS1* (69% and 38%, respectively).⁹ A 2017 retrospective study reported lower rates of large-panel testing. Of 814 patients with stage IIIB/IV NSCLC, 59% were tested for *EGFR* and *ALK* abnormalities. Only 8% underwent comprehensive genomic testing for all four major types of alterations (point mutations, indels, fusions, and copy number amplifications). Of those patients who did not receive testing, 13% did not have sufficient tissue for testing *EGFR/ALK* on initial biopsy.¹⁰

Both in the United States and globally, patients with NSCLC face challenges to receiving biomarker testing at many time points throughout their cancer journey. In many locations global access to health care facilities that can execute biomarker testing is limited. In the United States, a major barrier to widespread guideline adherence is the complexity of ordering biomarker testing and the interpretation of results, particularly in the community-based setting, where access to supportive resources such as molecular tumor boards (MTBs) and research protocols that allow for large next-generation sequencing (NGS) testing may be limited. Other challenges exist, including inadequate quantity or quality of tumor tissue, patients' lack of understanding and skepticism about the importance of testing, cost and reimbursement complexities, and institutional administrative barriers.

National Lung Cancer Roundtable Considerations

The National Lung Cancer Roundtable (NLCRT) is a United States-based coalition of professional societies,

government health agencies, advocacy groups, health plans, and industry groups convened by the American Cancer Society to focus on ensuring that those at high-risk of lung cancer have access to high-quality screening. The NLCRT also works to ensure that patients receive timely, patient-centered, state-of-the-art care for all stages of lung cancer (www.nlcrt.org). The NLCRT organizes work in focus-specific task groups across the various challenges that we face to reduce the burden of lung cancer. One task group, Triage for Appropriate Treatment (TAT), is charged with addressing the importance of guideline-adherent diagnosis and treatment, including by gathering data to better understand barriers to guideline-recommended care.

The TAT task group encourages health care providers treating patients with advanced or metastatic NSCLC to familiarize themselves with the updated recommendations published by CAP/IASLC/AMP and endorsed by ASCO.^{2,7} These guidelines recommend biomarker testing for patients with advanced or metastatic NSCLC with an adenocarcinoma component, the nonsquamous histological type, or any other histological type along with clinical features indicative of high risk of an oncogenic driver (e.g., younger age, no or light tobacco history).^{2,7} Biomarkers important to making treatment decisions that should be tested in at least single-gene assays include *EGFR* mutations and *ALK*, *ROS1*, and *BRAF* alterations. At a minimum, testing for these genes should be performed along with immunohistochemistry staining for programmed death ligand 1 (PD-L1). Guidelines for PD-L1 testing are forthcoming, but because immunotherapy options are currently guided by PD-L1 test results, it is important to assess this biomarker.² Additional biomarkers that should be included on an expanded lung cancer panel or with NGS should include erb-b2 receptor tyrosine kinase gene (*ERBB2* [also known as *HER2*]), MNNG HOS Transforming gene (*MET*), ret proto-oncogene gene (*RET*), and *KRAS*. Neurotropic tropomyosin receptor kinase gene (*NTRK*) is another important biomarker to assess, as patients with *NTRK* fusions may be treated with larotrectinib.¹¹ Microsatellite instability (MSI) should also be assessed when NGS testing is performed, as microsatellite instability–high tumors (independent of PD-L1 status) are eligible for second-line treatment with pembrolizumab monotherapy.¹² *EGFR* T790M mutations should be tested in patients who are treated with *EGFR* tyrosine kinase inhibitors other than osimertinib and whose tumor develops resistance to treatment. Importantly, although *EGFR*, *ALK*, *ROS1*, and *BRAF* are the only genes for which testing currently is required by the guidelines, expanded NGS panels allow maximum assessment of the patient's genomic landscape, which may provide the ability to identify rare abnormalities,

Table 1. List of Molecular Tumor Board Virtual and Print Resources for Providers

| Organization | Website/Journal |
|---|---|
| Healio Learn Genomics | https://www.healio.com/hematology-oncology/learn-genomics/tumor-boards/non-small-cell-lung/initial-diagnosis |
| ASCO Molecular Oncology Tumor Board | https://university.asco.org/motb |
| Association of Community Cancer Centers Virtual Molecular Tumor Boards: An Educational Series | https://www.accc-cancer.org/projects/virtual-tumor-boards/overview |
| Journal of Clinical Oncology Precision Oncology Molecular Tumor Board Case Discussion Series | http://ascopubs.org/journal/po |

ASCO, American Society of Clinical Oncology.

assess mutational tumor burden, and increase enrollment on clinical trials. There is emerging interest in mutational tumor burden and its relationship to immune checkpoint inhibitors. Programmed death 1/PD-L1 testing is imperative, as both squamous and non-squamous NSCLC are eligible for first-line immunotherapy treatment.

Challenges to Biomarker Testing Ordering, Reporting, and Interpretation of Biomarker Test Results

Health care providers are challenged with the task of keeping up with the plethora of newly discovered molecular targets and corresponding therapies. Leadership is needed to implement processes needed to support the providers. Educating health care providers is imperative. Oncologists need assistance for evaluating and selecting the appropriate tests for their patients and practice, explaining the science and potential (and often unpredictable) costs to the patients, and then executing the order. This can be a cumbersome and lengthy process, but it is possible even in community-based practices. A 2018 ASCO Educational Book article outlines strategies for implementing biomarker testing.¹³

The clinically acceptable turnaround time for receipt of biomarker testing results is 14 days, which is in alignment with guidelines.^{2,7} This period should also be regarded as an upper limit, because patients and providers desire speed in initializing treatment to improve efficacy.

Biomarker testing results should be stored in the electronic medical record in a reliable location for easy access by providers. Once results are received, difficulty interpreting the results may follow for several reasons, including lack of provider knowledge about reported abnormalities and how to treat them, scientific uncertainty about reported variants of unknown significance, and uncertainty about the best treatment approach among several potential options and sequencing. Provider participation in an MTB is ideal. Creating an MTB or finding one to join is essential to the best interpretation of biomarker test results. Commercial entities and

professional organizations offer some form of participation in MTBs (Table 1).

Financial Considerations for NGS Testing

In March 2018 the U.S. Centers for Medicare and Medicaid Services finalized a national coverage determination that approved coverage for NGS testing for recurrent or metastatic-stage III or IV lung cancer. The U.S. Centers for Medicare and Medicaid Services stated that NGS test results should be provided to physicians in a report template that specifies and simplifies treatment options.¹⁴ The CAP/IASLC/AMP recommends NGS over multiple single-gene tests because they can be completed faster and optimized for scant- or low-tumor content specimens. In newly diagnosed metastatic NSCLC, NGS has led to the same or shorter wait time for test results and the lowest payer cost.¹⁵ Testing of other gene mutations are likely to move into the frontline setting (e.g., *RET*, *NTRK*) and will make frontline NGS testing even more efficient and cost effective.

Specimen Adequacy

Another challenge to obtaining biomarker test results is specimen adequacy. A recent publication reported that up to 25% of submitted samples lacked sufficient tumor for testing.^{16,17} Dialogue is needed between multidisciplinary providers on the importance of obtaining a

Table 2. Guideline-Concordant, Recommended, and Optional Biomarkers in Patients with NSCLC

| Guideline-Concordant | Recommended | Optional ^a |
|-----------------------|-------------|-----------------------|
| EGFR, including T790M | | RET |
| ALK | MSI | MET |
| BRAF | PD-L1 | HER2 |
| ROS1 | NTRK | KRAS |
| | | TMB |

^aThese markers should be assessed as part of a large next-generation sequencing panel.

RET, ret proto-oncogene; ALK, ALK receptor tyrosine kinase; MSI, microsatellite instability; MET, MNG-HOS transforming gene; PD-L1, programmed death ligand 1; HER2, erb-b2 receptor tyrosine kinase; TMB, tumor mutational burden.

sufficient quantity and quality tissue for biomarker testing, not just for a histological diagnosis. The National Cancer Institute outlines suggestions to improve the quality of research biopsy specimens (Table 2). Institutionally, better understanding of the care path between tissue acquisition and delivery of test results to providers is needed.¹⁶ Dialogue is also needed to streamline approaches to getting the specimen prepared and shipped to expedite results. Blood-based biomarker evaluation methods (e.g., circulating tumor DNA) may be used as an alternative to assess *EGFR* and *T790M* status, especially when tumor tissue is limited.

Patient Awareness and Understanding

Patient awareness and understanding of the importance of testing at the time of diagnosis presents different challenges. The abundance of information available combined with the emotional aspect of their cancer diagnosis makes it easy for patients to feel overwhelmed and confused. A roundtable of patient advocacy groups and key leaders identified areas in which we could improve on education and communication with patients about biomarker testing.¹⁸ First, standardization of the language used to describe biomarker testing is urgently needed. The term *biomarker testing* was also referred to as molecular testing, genetic testing, genetic diagnostics, molecular diagnostics, and molecular pathways across patient education materials.¹⁸ The roundtable also recommended that educational efforts be focused on describing the who, what, when, where, why, and how of biomarker testing.¹⁸ Materials should be consistent, clear, customizable, and comprehensive. Regularly updated checklists containing questions that patients should ask their doctors should be made available to patients.¹⁸

Conclusions

The NLCRT TAT task group urges health care providers to prioritize the review of updated guidelines on biomarker testing. Additionally, increasing patient awareness and understanding may increase the likelihood of guideline concordant biomarker testing.

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