

***2013 Tumor Board Curriculum: Molecular Testing in Non-Small Cell Lung Cancer***  
Educational Grant

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## **PURPOSE**

The goal of this project is to ensure that pathologists, medical oncologists, radiation oncologists, surgical oncologists, interventional radiologists, pulmonologists, and other relevant healthcare professionals, including nurses have the knowledge and skills necessary to order, perform, and use the information acquired from biomarker testing to optimally manage patients with advanced NSCLC.

## **SCOPE**

Most patients with lung cancer are diagnosed with advanced non-small cell lung cancer (NSCLC). Currently, 5-year survival is only about 16% for patients with all stages of lung cancer and a dismal 4% for patients with metastatic disease.<sup>1</sup> However, recent data have shown that molecular testing can be used to select more effective treatment for patients with advanced disease and thus improve outcomes.<sup>2-4</sup> Using molecular tests to select targeted therapy has been shown to improve outcomes for patients carrying anaplastic lymphoma kinase (ALK) rearrangements and epidermal growth factor receptor (EGFR) mutations.<sup>5-7</sup> Crizotinib is effective in treating ALK rearranged tumors, and erlotinib is effective in tumors with activating mutations in EGFR, leading in recent years to dramatic responses in selected groups of patients treated with these drugs.<sup>5,6,8,9</sup> Crizotinib and erlotinib are oral tyrosine kinase inhibitors.<sup>4</sup>

Testing appropriate patients with advanced NSCLC for ALK rearrangements (also known as ALK gene fusions) or EGFR mutations is critically important to ensure delivery of the most effective lung cancer treatment.<sup>4,10,11</sup> Symptoms dramatically improve in patients with advanced nonsquamous NSCLC who receive either crizotinib or erlotinib, the oral therapy is easy to administer and tolerate, and severe side effects are rare.<sup>2,8</sup> Patients often quickly respond to crizotinib and have prolonged progression-free survival.<sup>6,9</sup> Currently, crizotinib and erlotinib are the only treatment options for patients with ALK rearrangements and EGFR mutations in the United States. Clinical utility is a risk/benefit assessment that can be used to determine whether molecular testing should be adopted. Molecular testing for ALK rearrangements and EGFR mutations has clinical utility because the benefits of testing exceed the risks.<sup>3,12,13</sup> The NCCN Guidelines for NSCLC currently recommend testing for ALK rearrangements and EGFR mutations in patients with advanced nonsquamous NSCLC ([www.nccn.org](http://www.nccn.org)).<sup>3</sup> However, many patients are not being offered molecular testing because of gaps in the management and education of patients with advanced nonsquamous NSCLC.

The NCCN proposes a series of webinars specifically developed to educate physicians involved in the diagnosis and treatment of NSCLC patients including pathologists, medical oncologists, radiation oncologists, surgical oncologists, interventional radiologists, and pulmonologists, as well as patient navigators about the value of molecular testing in advanced nonsquamous NSCLC.<sup>14</sup> Gaps in awareness of the need for molecular testing and in the practical considerations of implementing and interpreting testing can be addressed by this educational program. Identified practice gaps include insufficient or inappropriate tissue samples (for example, necrotic samples), excessive turnaround times for testing, and inefficient use of tissue for testing, which decreases the amount available for molecular assessment.<sup>4,15</sup> Although multidisciplinary cooperation is key to the global treatment of these patients, some issues are of primary concern to one group of clinicians or another. The webinars will include a mock tumor board to illustrate the multidisciplinary cooperation required to optimally manage NSCLC

patients and will be targeted to a multidisciplinary audience. Another webinar will address tissue acquisition with surgeons and interventional radiologists being the primary audience. A third will address biomarker test selection and validation with pathologists being the primary audience. A fourth will focus on patient education needs with patient navigators and oncology nurses being the primary audience. Major practice gaps will be identified in each of these programs and solutions to remedy the gaps based on experience at comprehensive cancer centers (that is, NCCN Member Institutions) will be presented.

#### *Role and Information Needs of the Pathologist Assessing Non-Small Cell Lung Cancers*

Pathologists are an integral part of the multidisciplinary process of managing patients with NSCLC. As the use of biomarkers in lung cancer has become more sophisticated, the role of the pathologist has become pivotal in clinical decision making for this disease. Actionable molecular assays are now available which may guide treatment decisions for NSCLC.<sup>3</sup> The pathologist needs to know which biomarkers have clinical utility. Also, the pathologist must know which tests and test kits are reliable, which assays can be done in house, and which can be sent to a central laboratory. Issues of analytic validity and clinical validity are also important to the selection, use, and evaluation of novel biomarker tests as they become available.

In NSCLC management, biomarkers supplement traditional histologic classification and staging studies to refine diagnosis and treatment paradigms. Three markers have actionable clinical relevance in management of this disease: EGFR mutations, KRAS mutations, and ALK rearrangements. Several methods are available for testing for EGFR mutations.<sup>21</sup> The current NCCN Guideline for NSCLC does not recommend a particular method, noting only that mutation testing is preferable to either 1) FISH assessment of EGFR copy number, or 2) immunohistochemistry to assess EGFR protein levels (<http://www.nccn.org>).<sup>22-24</sup> Several studies analyzing both EGFR and KRAS mutations have shown that the two mutations are present in mutually exclusive populations.<sup>25-27</sup> FISH and immunohistochemistry have both been used to detect ALK rearrangements, and some clinicians suggest confirming mutation status using both assays.<sup>10,20</sup> However, testing for ALK rearrangements by FISH is the only FDA-approved ALK test available at this time. Detailed guidelines for EGFR and ALK testing in lung cancer are in progress, which are a collaborative effort among CAP (College of American Pathologists), AMP (Association for Molecular Pathology), and IASLC (International Association for the Study of Lung Cancer).<sup>15</sup> These guidelines should be a valuable resource for guideline developers and practitioners. A number of additional somatic mutations are detected in lung cancer, and molecular tests for them may enter clinical practice for NSCLC in the near future. These include mutations in BRAF, HER2 (ERBB2), AKT1, MAP2K1 (MEK1), and PIK3CA; gene amplifications in MET; or fusions involving the ROS tyrosine kinase. Each of these is present in a small percentage of lung cancer patients (1%-5%) and will require further validation before general use to direct treatment.<sup>28</sup>

Pathologists face a number of issues when incorporating biomarker testing into their work flow. Some of the challenges to clinical adoption include assay variability and inadequate analytic validation, poor study design and analysis, and inadequate reporting,<sup>29-35</sup> as well as practical obstacles (such as lack of resources, personnel, or expertise in smaller clinical laboratories). In addition, the pathologist needs to work closely with the surgeon or the interventional radiologist to ensure that adequate tissue is available to perform the assays. Since identification of

biomarkers is most relevant in the metastatic setting, obtaining sufficient biopsy material to perform a series of tests can be challenging. Pathologists must make decisions about which tests should have priority based on likelihood of an actionable result.

In addition, an increasing number of multi-analyte tumor markers require comprehensive technologies and computational algorithms but hold promise in situations like metastatic NSCLC where limited tissue is available for analysis. However, these platforms and analytic approaches may only be available at major cancer centers and represent challenges to independent validation and verification.

The pathologist must also understand the concepts of analytic and clinical validation which are used to identify the specific tests that are most reliable and informative.

*Analytic Validation.* Analytic validation focuses on determining how accurately and reliably the assay measures the molecular event of interest.<sup>33,35,36</sup> Even assays that are routinely performed in the laboratory require analytic validation within a clinical laboratory setting in order to be used to make clinical decisions. Results can be influenced by various factors, both within and outside of the control of the pathology laboratory. Clinical laboratories should understand the effect that pre-analytic variables and specimen processing have on assay performance so as to ensure reproducible findings.

*Clinical Validation.* Clinical validation assesses the strength of association between the assay results and the clinical outcome of interest; be it diagnostic, prognostic, or predictive. Many measures are used to assess these associations. These analyses assess questions such as; if the test is positive, can we be sure that the clinical state is positive (positive predictive power)? If the test is negative, can we be sure that the clinical state is negative (negative predictive power)?

#### *Role and Information Needs of Non-Pathologist Physicians Involved in the Diagnosis and Treatment of NSCLC Patients*

A wide variety of clinicians need to work together to treat NSCLC patients including medical oncologists, radiation oncologists, surgical oncologists, interventional radiologists, and pulmonologists. Minimally invasive techniques to obtain biopsy samples (e.g., endobronchial ultrasound-guided transbronchial needle aspirates [EBUS-TBNA]) may be preferable for patients with advanced NSCLC who are not surgical candidates or those who require additional biopsies.<sup>4,10,11</sup> Studies show that ALK gene rearrangements and EGFR mutations can be detected using these small tissue samples.<sup>10,11</sup> Accurate determination of histology is essential for molecular testing. Although ALK rearrangements and EGFR mutations are rare, they tend to occur in patients with nonsquamous NSCLC.<sup>10,16</sup> In addition, ALK rearrangements and EGFR mutations are mutually exclusive.<sup>5,17</sup> The NCCN Guidelines for NSCLC recommend that patients with adenocarcinoma or large cell carcinoma histology (that is, nonsquamous NSCLC) should have molecular testing for ALK gene rearrangements and EGFR mutations (<http://www.nccn.org>).<sup>11,18</sup>

ALK rearrangements can be detected using the FDA-approved ALK break-apart fluorescence in situ hybridization (FISH) probe test, which is considered the gold standard because it was a

requirement for enrolling patients on clinical trials for crizotinib.<sup>18</sup> However, recent data suggest that the ALK FISH probe test may not detect all patients with ALK rearrangements.<sup>19</sup> Immunohistochemistry or RT-PCR may be more accurate.<sup>18,19</sup> One solution to this dilemma is to screen appropriate patients with nonsquamous NSCLC for possible ALK rearrangements using immunohistochemistry; positive immunohistochemistry results can then be assessed and confirmed using the ALK break-apart FISH probe test and/or reverse transcriptase—polymerase chain reaction (RT-PCR).<sup>10,20</sup> Thus, molecular testing of ALK rearrangements is evolving and clinicians should be aware of the latest developments. Results of these tests are key to the selection of optimal systemic therapy for NSCLC patients by the medical oncologist.

#### *Role and Information Needs of Patient Navigators in Non-Small Cell Lung Cancer*

Oncology Patient Navigators are professional nurses or healthcare professionals who have experience working with people with cancer and understand their challenges. Patient navigators may also be called care managers, case managers, or be referred to by other titles. Navigators help remove roadblocks to treatment, so that patients are able to keep their appointments, follow their treatment regimens, and receive the support services they need. Navigator goals<sup>37</sup> include:

- Educating, advocating for, and helping cancer patients navigate the complex medical world throughout the entire course of cancer treatment and beyond.
- Improving patient outcomes by working to eliminate barriers to care.
- Being a central point of contact for information about cancer resources and community support services.
- Serving as the cancer patient's personal care coach.

Patient navigators may work in a variety of settings. Most work directly with patients in academic and community cancer centers or oncology practice settings. Others work in managed care organizations, where they work with patients telephonically. Navigators in most settings do not work exclusively with lung cancer patients, with those working in academic cancer centers being the most likely exception. Rather, they most often work with patients that have a variety of different types of cancer. Regardless of setting, these navigators need to keep abreast of advances in clinical knowledge and their application to individual patients. The fact that most do not focus exclusively on lung cancer makes it even more challenging to stay current on new clinical developments.

Additionally, nurses in all types of roles, including nurse navigators, are challenged to find the time and organizational support to attend clinical conferences and programs. Access to educational content that is targeted to their needs is highly valued, especially when the educational programming is convenient and affordable.

As described elsewhere in this proposal, the treatment of NSCLC now requires clinicians to know the results of molecular assays in order to provide the most effective treatment. Patient navigators need to be able to understand these requirements and be able to explain to patients why additional testing is important and why not all lung cancers are the same. Knowledge in this area is highly technical and is increasing at a rapid pace, posing a significant challenge for physicians and other healthcare professionals alike. In order to be an effective member of the patient care team, a patient navigator must keep up to date on new knowledge that has direct implications for patient education and patient care.

### *Information Needs of the Patients with Non-Small Cell Lung Cancer*

Health information can be overwhelming. To address this challenge, NCCN uses many strategies to create user-friendly patient education handouts. The NCCN Guidelines for Patients® and handouts based on these NCCN Guidelines for Patients will provide patients with the same information that cancer professionals receive from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) in patient-friendly formats.

One of the most important strategies is the application of plain language principles. Plain language is communication that users can understand the first time they read or hear it.<sup>41</sup> The major principles of plain language include targeting the audience, good organization, and a clear writing style.

Inclusion of definitions is another strategy used to help readers comprehend the material. Words that readers may not know will be defined in the text or a sidebar. Words with sidebar definitions are underlined when first used on a page. The sidebar also may contain cross-references to other pages with more information and the full name of acronyms as space permits. A dictionary of all defined terms is included in the NCCN Guidelines for Patients®.

Just as important as the writing style, the graphic design of the handouts will aim to increase usability and comprehension. Clinical images will be included to help readers learn about cancer, cancer tests, and treatments. Photography is also added to enliven the handouts and hold readers interest. A typography will be chosen based on its readability. Readability is also addressed by short text lines, sufficient white space, and appropriate use of color.

Health literacy is defined as “the ability to obtain, process, and understand basic health information and services needed to make appropriate health decisions.”<sup>38</sup> According to the National Assessment of Adult Literacy, 90% of adults have limited health literacy.<sup>39</sup> Low health literacy negatively affects people’s ability to find and use health information. It has also been linked to poor health outcomes such as more severe illness at initial workup, poorer self-management of illness, and greater use of emergency medicine.<sup>40</sup>

Health literacy involves not only reading and comprehension skills but cognitive abilities to obtain, process, and respond to information. Molecular testing for NSCLC is a relatively new requirement that not all health care professionals—let alone patients—know about. The provision of patient education handouts aims to empower patients. The handouts will promptly provide patients with current information and will be designed in a patient-friendly format to increase usability and comprehension. As such, the patient education handouts can help with information exchange and shared decision-making between professionals and patients. The end result will likely be improved health outcomes, such as extended survival.

Many people lack knowledge or have misinformation about their body, diseases, and treatment. The NCCN Guidelines for Patients® address all these topics. Patients are taught the basic anatomy of the lungs and that lung cancer is a disease of cells. To understand molecular testing, biopsy tests are described, and patients are alerted that more than one biopsy may be done to collect adequate amounts of tissue. Furthermore, explanations of genes, EGFR and ALK gene

mutations, and cell receptors are given as an essential preface to explaining targeted therapy. Information on targeted therapy includes the mechanisms of drugs and the NCCN recommendations of use.

NCCN proposes to develop a stand-alone patient education piece using these principles describing the need for and mechanics of biomarker testing and its implications for treatment selection. Patient awareness of the need for molecular testing is critical for success. Patients need to understand that testing for ALK rearrangements and EGFR mutations is beneficial because targeted therapy has been shown to dramatically improve outcomes. Patients should know that crizotinib and erlotinib are very effective oral agents with low toxicity; these agents often improve symptoms and are associated with prolonged progression-free survival.

### *Learning Objectives*

Following this program, participants should be able to:

- Describe the respective contributions made by various multidisciplinary team members to the management of NSCLC
- Discuss the molecular testing considerations for patients with ALK rearrangements and EGFR mutations
- Discuss the considerations and challenges of obtaining appropriate tissue samples
- Develop core communication messages for use with patients in advance of testing decision making
- Describe the appropriate selection of therapies for patients with NSCLC using biomarker data.
- Discuss the optimal evaluation and workup of patients with NSCLC.

*Target Audience:* This educational program is designed to meet the educational needs of physicians, nurses, pharmacists, and other healthcare professionals who manage patients with cancer. The physician target audience will include a wide variety of physicians involved in the diagnosis and treatment of NSCLC patients including pathologists, medical oncologists, radiation oncologists, surgical oncologists, interventional radiologists, and pulmonologists. The program will also meet the educational needs of NSCLC patient navigators. While not our primary audience, patients are an indirect target audience for this educational initiative.

This activity will meet the following clinician competencies:

- IOM: Employ evidence-based practice
- ACGME/ABMS: Demonstrate medical knowledge
- ACPE: Practice evidence-based medicine; deliver patient-centered care
- ANCC: Demonstration of a learned skill and implementation of that skill in practice/healthcare setting

## **METHODS**

NCCN plans to offer six (6) live webinars on below topics:

- Interdisciplinary cooperation: A Model Tumor Board in NSCLC
- Tissue Acquisition in NSCLC: Surgical and Interventional Radiology Perspectives
- Best Practices in Molecular Testing in NSCLC
- Patient Navigation: Role in Molecular Testing in NSCLC Appropriate Selection of Therapy in NSCLC Using Biomarker Data

- Evaluation and Workup of Patients with NSCLC

Each webinar will be presented once and will consist of slides and audio. Each webinar will be certified for continuing education credits for pharmacists. NCCN anticipates a minimum of 100 learners per webinar, for a total of 600 learners participating in six webinars.

*Description of Program*

NCCN plans to launch a live webinar stream, consisting of slides, audio, and video with a discussion board following each one of the webinars. Webinar attendees may access a free one-month subscription to the NCCN Biomarkers Compendium® within a sixty-day window following the webinar in which they participate.

In order to extend the reach of this program, NCCN will archive the session from this activity in NCCN's new Learning Management System, <http://education.nccn.org>. These archived enduring materials will offer credit and will be placed on the NCCN web site within a few weeks of the date of the live webinar.

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**RESULTS**

The proposed educational activity will result in Level 5 outcomes, according to Moore's 2009 expanded outcome framework. Level 5 is defined by Moore as the degree to which participants do what the CME activity intended them to be able to do. To measure the effectiveness of this activity, NCCN's outcome measurement will collect self-reported data on clinician application of content from the educational activity to practice and change in practice.

NCCN will collect data through various instruments: the pre-activity survey, the activity evaluation, an immediate post-test, a 30-day post-test, and a post-activity follow-up survey. The pre-activity survey will measure baseline practice. The evaluation and follow-up survey will ask learners, at different time intervals, what they are doing in their practice at that later point in time. Analysis of this information will determine whether a practice change/performance improvement has occurred.

The target measures for success will be individual comparisons of pre-program practice and post-program practice. Increases or improvements in self-reported performance will measure success. The value of the program will be extended through electronic slide decks in NCCN's learning management for attendees' use.