

Examining Biomarkers and the Pulmonologist's Role in Lung Cancer Treatment

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Biomarker Use for Pulmonologists: Pulmonary Nodule Management

Introduction

In the United States, it is estimated that pulmonary nodules are detected in up to 1.6 million patients each year. Detection of incidental pulmonary nodules has risen due to both increased use of chest CT scanning and more frequent nodule detection on these scans, and that the former appears to play a more significant role.¹ While most pulmonary nodules are benign, the task of the clinician is to distinguish benign from malignant nodules. Management options include watchful waiting with surveillance imaging, functional imaging (eg, PET-CT scan), non-surgical biopsy, surgical biopsy, or empiric therapy with radiation or ablation. Decision-making is based on a nodule's pre-test probability of malignancy via clinical judgment and/or validated nodule malignancy calculators. More invasive strategies are reserved for higher risk nodules (**Table 1**).² Unfortunately, there is significant variability in practice patterns, and some patients with low-risk nodules are undergoing invasive procedures.³ Management of "intermediate-risk" nodules is particularly-challenging as a significant portion will be malignant, and additional tools to place "intermediate" risk nodules into the "high" or "low" risk categories would be clinically beneficial. Recent updates to clinical guidelines emphasize the importance of risk assessment tools and the emergence of biomarkers that may improve risk stratification.

Pulmonary nodule management includes 1) assessing a nodule's risk of malignancy, 2) engaging in shared decision-making, and 3) choosing the best management path for an individual patient. This review article lays out the challenges pulmonologists face as they manage incidental pulmonary nodules and how biomarkers have the potential to improve nodule management decisions. We will also review key portions of 3 important clinical guidelines, summarize 3 biomarker trials that have the potential to change practice, and speculate at what lies ahead as emerging biomarkers are tested, assessed, and make their way into pulmonology practice. An important note is that the majority of this article is focused on *incidental* pulmonary nodules. Nodules detected in the process of lung cancer screening are most generally managed

TABLE 1: Factors that influence choice between evaluation and management alternatives for indeterminate, solid nodules ≤8 to 30 mm in diameter²

Factor	Level	CT Scan Surveillance	PET Imaging	Nonsurgical Biopsy	VATS Wedge Resection
Clinical probability of lung cancer	Very low (<5%)	++++	-	-	-
	Low-moderate	+	+++	++	+
	High (<65%)	-	(± staging)	++	++++
Surgical Risk	Low	++	++	++	+++
	High	++	+++	++	-
Biopsy Risk	Low	-	++	+++	+++
	High	++	+++	-	+
High suspicion of active infection or inflammation		-	-	++++	++
Values and preferences	Desires certainty	-	+	+++	++++
	Risk averse to procedure-related complications	++++	+++	++	-
Poor adherence with follow-up		-	-	+++	++++

Reprinted from Gould M, Donington J, Lynch W, et al. Evaluation of individuals with pulmonary nodules: When is it lung cancer? *CHEST*. 2013;143(5):e93S-e120S.

Abbreviations: CT, computerized tomography; PET, positron emission tomography; VATS, video-assisted thoracic surgery.

via appropriate algorithms (eg, Lung-RADS), and few data regarding biomarker use in lung cancer screening have been published.

The Challenge for Pulmonologists

Pulmonary nodules are regularly encountered in the typical pulmonary practice. While the majority are benign, pulmonologists are nonetheless presented with the challenge of accurately identifying and managing those that are not. What's more, true incidence of pulmonary nodules may be much higher than previously assumed. Review articles had suggested that 150,000 nodules are detected in Americans each year. Often-cited older studies report incidence rates of between 0.1% and 0.2%. However, given the increased frequency of chest imaging, particularly via CT scanning, the actual numbers may be much higher. Based on a cohort study published in 2015, investigators estimated that incidental pulmonary nodules are found in more than 1.6 million Americans each year via chest radiograph or thoracic CT scan. Moreover, the analysis suggests an incidence rate of 1.7%. Hence, the proverbial needle is in a much larger haystack.¹

Since most pulmonary nodules are benign, it is imperative to find the right point at which an invasive procedure results in identification and treatment of malignancy, while avoiding interventions for those nodules that are benign.⁴ The rise in pulmonary nodule detection—driven mainly by increased use of CT scans—is accompanied by significant challenges. First, though American College of Chest Physicians (CHEST) guidelines provide standardized recommendations for estimating the pretest probability of malignancy (pCA) to guide nodule management, practice patterns vary widely. Evidence suggests that the recommendations are not followed by many, leading to unnecessary intervention for benign nodules.³ Second, though a nodule's risk of malignancy can

be estimated via well-established patient characteristics (including age, smoking history, and malignancy history) and imaging characteristics (including nodule size, location, and edge characteristics), these tools are imperfect.⁵ Third, multiple nodule risk assessment tools to estimate probability of malignancy are available, and an individual's pCA differs between models.⁶ Similarly, multiple society guidelines exist to provide clinical guidance. Finally (and most concerning), many providers pursue invasive evaluations for low risk nodules. Reviewing the available guidelines and recent literature should provide some clarity on these topics.

Summary of Key Guidelines

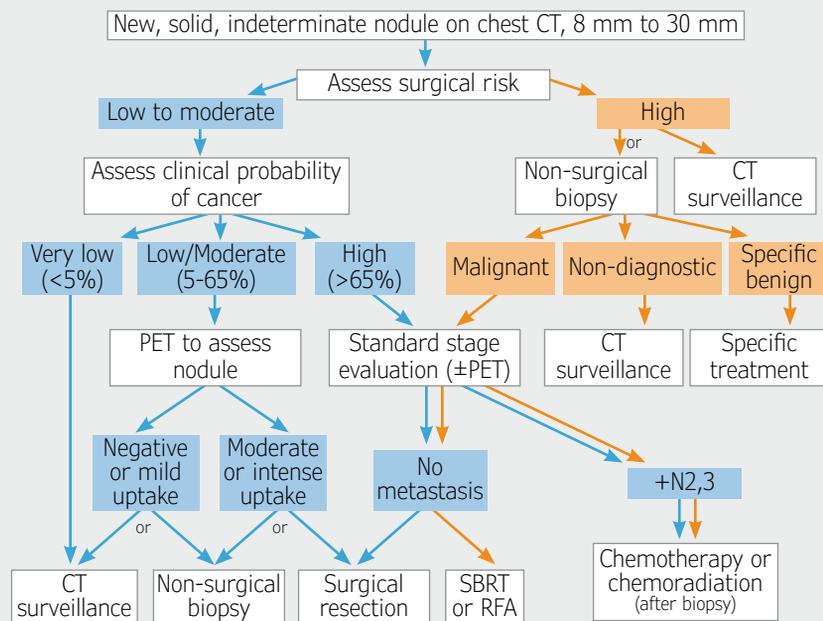
American College of Chest Physicians

CHEST's "Evaluation of Individuals with Pulmonary Nodules: When Is It Cancer?" from the organization's guideline, *Diagnosis and Management of Lung Cancer*, includes recommendations for evaluating solid and non-solid nodules with an emphasis on estimating pCA. The guideline includes parameters for when pretest probability of malignancy is very low (<5%), moderate (5% to 65%), or high (>65%; see **Figure 1**).²

CHEST guidelines provide recommendations for nodule management based on nodule size and solidity. Among the recommendations for solid pulmonary nodules >8 mm:

- Estimate pCA using clinical judgment or a validated model.
- In nodules with a high pCA (>65%), functional imaging (eg, PET/CT) should not be obtained to further characterize the nodule (it may be obtained for staging to evaluate for metastasis).
- Employ surveillance CT when pCA is <5%; or, when pCA is <30% to 40% and functional imaging results are negative.

FIGURE 1: Management algorithm for individuals with solid nodules measuring 8 to 30 mm in diameter



Reprinted from Gould M, Donington J, Lynch W, et al. Evaluation of individuals with pulmonary nodules: When is it lung cancer? *CHEST*. 2013;143(5):e93S-e120S.

Abbreviations: CT, computerized tomography; PET, positron emission tomography; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy.

- The frequency and length of time between scans depends on the patient and nodule characteristics.
- When serial imaging reveals a growth pattern consistent with malignancy, perform non-surgical biopsy and/or surgical resection.
- Perform nonsurgical biopsy when 1) pCA and imaging findings are not concordant; 2) when pCA is at intermediate risk; and 3) when a benign diagnosis nonetheless needs to be treated.
- Perform surgical biopsy—preferably via thoracoscopy—when 1) pCA is >65%; 2) PET shows the nodule to be hypermetabolic; and 3) nonsurgical biopsy reveals a suspected malignancy.²

Among the recommendations for pulmonary nodules ≤8 mm:

- When there are no risk factors for lung cancer, with regard to CT surveillance:
 - There is no need for routine follow-up for nodules ≤4 mm.
 - Reevaluate nodules >4 mm to 6 mm at 12 months; no need for follow-up if unchanged.
 - Reevaluate nodules >6 mm to 8 mm at 6 to 12 months, and, if unchanged, again at 18 to 24 months.
- When the individual has ≥1 lung cancer risk factor, with regard to CT surveillance:
 - Reevaluate nodules <4 mm at 12 months; no need for follow-up if unchanged.
 - Reevaluate nodules >4 mm to 6 mm at 6 to 12 months, and, if unchanged, again at 18 to 24 months.
 - Reevaluate nodules >6 mm to 8 mm at 3 to 6 months,

and, if unchanged, again at 9 to 12 months and at 24 months.²

Among the recommendations for nonsolid (pure ground-glass) nodules:

- There is no need for routine follow-up to evaluate nodules ≤5 mm.
- Employ annual surveillance CT for at least 3 years when nodules are >5 mm.²
- Among the recommendations for part-solid (>50% ground-glass) nodules:
 - Employ surveillance CT at 3, 12, and 24 months in nodules ≤8 mm, with annual surveillance thereafter for 1 to 3 years.
 - Repeat CT at 3 months when nodules are >8 mm, followed by further evaluation with PET, nonsurgical biopsy, and/or surgical resection for persistent nodules.²

British Thoracic Society

The British Thoracic Society (BTS) Guidelines for the Investigation and Management of Pulmonary Nodules includes 4 management algorithms and utilizes 2 malignancy prediction calculators. Whereas the CHEST guidelines prioritize nodule diameter, BTS relies on volumetric measurements for risk assessment and provides guidance on further imaging.⁷ Similar to CHEST, BTS guidelines risk stratify nodules (low risk <10%, intermediate risk 10-70%, high risk >70%) and recommend less invasive strategies for low risk nodules.

Among the recommendations regarding initial assessment using a volumetric strategy:

- Do not perform nodule follow-up for nodules <5 mm or <80 mm³ volume.
- Employ surveillance CT when nodule is ≥5 mm to <8 mm or ≥80 mm³ to <300 mm³.
- Employ the Brock model for initial risk assessment when nodule is >8 mm or >300 mm³ in patients ≥50 years of age.
- Consider the Brock model for all patients with nodules of this size.
- Use composite prediction models to estimate probability of malignancy in nodules >8 mm or >300 mm³.⁷

Among the recommendations regarding imaging follow-up for low-risk nodules, including use of volume doubling time (VDT):

- Employ interval CT to assess nodule growth rate in nodules assigned a <10% risk of malignancy during initial assessment.
- Calculate VDT based on repeat CTs performed at 3 months and 1 year to assess nodule growth >80 mm³ or ≥6 mm.
- Calculate VDT based on repeat CT at 1 year to assess nodule growth ≥5 mm to <6 mm.
- Offer biopsy, imaging, or resection for nodules that show clear growth or VDT <400 days (assessed after 3 months and 1 year).
- Perform no further assessment for nodules that remain stable on CT after 1 year.

- Consider yearly surveillance or biopsy for nodules with a VDT of 400 to 600 days.
- For nodules with a VDT >600 days, choose between no further assessment or surveillance at 1 year, based on patient preference, fitness, and age.⁷

Among the recommendations regarding imaging follow-up for medium- and high-risk nodules:

- Offer PET-CT scan for pulmonary nodules with an initial malignancy risk via Brock of $\geq 10\%$ where nodule size is greater than the local device's detection threshold.
- After reassessing risk in these individuals via Herder prediction tool:
 - Consider image-guided biopsy for nodules with a 10% to 70% malignancy risk. Other options—considering patient preference and individual risk—are excision biopsy or CT surveillance.
 - Offer surgical excision for nodules with a >70% malignancy risk. Consider other options for nonsurgical candidates.⁷

Fleischner Society

The 2017 Fleischner Society Guidelines for the Management of Incidental Pulmonary Nodules Detected on CT Images provide updated recommendations on the management of both solid and subsolid nodules.⁸

For solid nodules:

- The minimum threshold size that should trigger routine follow-up has increased to 6 mm. This change is based on trial results showing that nodules <6 mm carry a less than 1% risk of cancer, even in high-risk individuals. Since risk can be higher in some cases—specifically nodules with suspicious morphology and/or upper lobe location—consider follow-up at 12 months but no sooner in such instances. Small nodules, if malignant, do not often advance in stage over 12 months. No change in nodule size during shorter follow-up can cause false assurance.
- It is acceptable to discontinue follow-up of well-defined benign nodules at 12 to 18 months if the nodules are deemed stable.⁸

For subsolid nodules:

- Follow-up for pure ground-glass nodules ≥ 6 mm is recommended at 6 to 12 months, and every 2 years after that until 5 years. The previous recommendation was for follow-up at 3 months, but that is not likely to change outcome of these nodules.
- For those that are ≥ 6 mm with a solid portion measuring <6 mm in diameter, follow-up is suggested at 3 to 6 months, then annually **for at least 5 years**. When the solid component is small, risk of invasive adenocarcinoma is minimal. Additionally, partially solid nodules could be due to transient infection that resolves over time.⁸

The Emergence of Biomarkers

Though management of nodules in the low- and high-risk categories are clear, the management of intermediate-risk nodules remains a challenge. Many of these nodules will ultimately prove to be cancer, yet pulmonologists should strive to avoid invasive evaluations for those patients with

benign lesions. Biomarker testing holds promise for providing more effective risk assessment.

Though BTS makes additional recommendations regarding the use of non-imaging tests and nonsurgical biopsy, (eg, when to use bronchoscopy, when to augment bronchoscopy and what to use, when to offer percutaneous lung biopsy, and when to employ other imaging techniques), the BTS guidelines do not advise the use of biomarkers in the assessment of pulmonary nodules.⁷ Notably, the BTS recommendations were published prior to important studies demonstrating the potential value of select biomarkers. Thus, this technique deserves to be reconsidered, especially in light of the fact that evidence demonstrates that guidelines are often not followed, leading to unnecessary intervention.¹ We provide a summary of 3 studies evaluating biomarker use: 1) a protein-based biomarker panel follow to assess for an *individual's* lung cancer risk; 2) a bronchial airway gene-expression classifier in indeterminate pulmonary nodules; and 3) an integrated proteomic classifier in indeterminate pulmonary nodules.

INTEGRAL Consortium Evaluates Protein-based Biomarker Panel

In distinction from most studies in this article that evaluate a *nodule's* risk of malignancy, the INTEGRAL Consortium for Early Detection of Lung Cancer published data demonstrating that a risk prediction model utilizing a protein-based biomarker panel could improve assessment of an *individual's* lung cancer risk. More specifically, biomarker testing could more accurately define CT screening criteria. These findings are potentially useful given that the US Preventive Services Task Force (USPSTF) recommends CT screening for lung cancer in current or former smokers meeting lung cancer criteria.⁹

The analysis involved development and validation cohorts of ever-smoking participants with lung cancer and smoking-matched controls. In the 2 development cohorts, samples were taken from ever-smoking (n=108) and control (n=216) contingents to work up a biomarker score based on circulating measures of several proteins. Researchers subsequently assessed the score in 2 validation cohorts of ever-smoking patients (n=63) and matched controls (n=90). Among the results:

Accuracy vs traditional smoking-based risk tool: When using the integrated risk prediction model, risk assessments increased for cases (from 0.27% [interquartile range (IQR), 0.14% to 0.50%] to 0.45% [IQR, 0.18% to 1.5%]) and decreased for controls (from 0.12% [IQR, 0.05% to 0.21%] to 0.04% [IQR, 0.15% to 0.17%]).

Sensitivity and specificity: Using USPSTF screening criteria, the integrated and smoking models produced sensitivities of 0.63 (95% Confidence Interval [CI], 0.49 to 0.75) and 0.43 (95% CI, 0.23 to 0.65), respectively, and specificities of 0.95 (95% CI, 0.85 to 0.99) and 0.86 (95% CI, 0.72 to 0.94), respectively.

The investigators concluded that 1) use of the integrated biomarker tool appears to be capable of detecting more individuals who eventually develop lung cancer that should

be referred for CT screening, and 2) the tool could also be used to lower the number of screened individuals who eventually do not develop lung cancer.⁹

AEGIS Trials Evaluate Bronchial Airway Gene-Expression Classifier

In 2015, results of a large prospective multicenter trial demonstrated that a bronchial airway gene-expression classifier improves the diagnostic accuracy of bronchoscopy in the detection of lung cancer. Moreover, the classifier indicated that a more conservative diagnostic approach could be taken in patients at intermediate risk with a nondiagnostic bronchoscopic examination.¹⁰

Participants included current or former smokers who underwent bronchoscopy at 28 centers in 3 countries, including the United States. Prior to bronchoscopy, treating physicians evaluated each participant's pretest probability of having cancer. At the time of bronchoscopy, investigators collected epithelial cells, then followed participants until a diagnosis was made or until 12 months post-bronchoscopy. Patients diagnosed with lung cancer and those determined to be cancer-free—639 individuals in total—were included in the analysis. Among the results:

- *Patient characteristics:* In 2 validation sets, AEGIS-1 (n=298) and AEGIS-2 (n=341), lung cancer prevalence rates were 74% and 78%, respectively. Forty-three percent of the bronchoscopies in both cohorts were nondiagnostic [95% CI, 38 to 46), including 120 patients who ultimately received a lung cancer diagnosis. Sensitivity for bronchoscopy-alone in the detection of lung cancer was 74% (95% CI, 68 to 79) in AEGIS-1 and 76% (95% CI, 71 to 81) in AEGIS-2.¹⁰
- *Bronchoscopy performance:* Among patients with post-bronchoscopy procedure data available (n=267), 64% underwent a subsequent invasive procedure, including 52 of 147 who had benign lesions and 118 of 120 who had cancer. Seventy-six individuals underwent surgical lung biopsy, including 27 whose lesions were benign.¹⁰
- *Gene-expression classifier performance:* Combining the classifier and bronchoscopy improved the sensitivity in AEGIS-1 to 96% (95% CI, 96 to 99), vs 74% for bronchoscopy alone. In AEGIS-2, sensitivity was 98% (95% CI, 96 to 99) and 76%, respectively. As for patients with nondiagnostic bronchoscopies, the classifier identified cancer in 49 of 57 AEGIS-1 patients (86% sensitivity; 95% CI, 74 to 94) and 58 of 65 AEGIS-2 patients (92% sensitivity; 95% CI, 82 to 97).¹⁰
- *Subgroup analysis:* Bronchoscopy alone was not as sensitive for smaller lesions, those that were peripherally located, or those in patients without hilar or mediastinal adenopathy. The classifier alone and in combination with bronchoscopy resulted in consistently high sensitivity regardless of lesion size and location, cancer stage, histologic type of cancer, or adenopathy existence.¹⁰
- *Classifier accuracy in patients with intermediate risk of cancer:* Among 101 individuals with a pretest probability of having an intermediate risk of cancer, bronchoscopy was nondiagnostic in 83% (41% were eventually diagnosed with cancer). The classifier had a negative

predictive value of 91% (95% CI, 75 to 98) and a positive predictive value of 40% (95% CI, 27 to 55).¹⁰

The investigators concluded that a gene-expression classifier can help exclude patients whose lesions are found to be benign from further invasive testing, given its high negative predictive value in those with intermediate probability of disease and a nondiagnostic bronchoscopy.¹⁰

PANOPTIC Trial Evaluates Integrated Proteomic Classifier

In 2018, the findings of a prospective multicenter observational trial showed that a protein-based blood test accurately identifies benign lung nodules, thus carrying the potential to spare many individuals with such nodules from invasive follow-up.¹¹

Treating physicians assessed pretest pCA in participants with lung nodules measuring 8 to 30 mm in diameter. Blood samples were then merged with participant risk factors, producing a posttest probability of a lung nodule being benign. The analysis focused on patients with a $\leq 50\%$ pCA (n=178), 16% of whom were ultimately found to have lung cancer. Among the results:

- *Accuracy vs established stratification methods:* The integrated proteomic classifier had a sensitivity rate of 97% (95% CI, 82 to 100), a specificity rate of 44% (95% CI, 36 to 52), and a posttest probability rate of 98% (95% CI, 92 to 100), outperforming established lung cancer nodule risk stratification models.¹¹
- *Classification accuracy:* The integrated classifier categorized 66 participants as "likely benign." All but 1 had benign nodules. Given that 149 benign and 29 malignant nodules were evaluated in the study, 44% of benign nodules (65 nodules) were accurately classified, and 3% of malignant nodules (1 nodule) were not. Among 58 participants who underwent an invasive procedure after initial detection, 35 were benign and 23 were malignant. Forty percent of the benign nodules (14 nodules) were correctly identified by the integrated classifier, and 4% of the malignant nodules (1 nodule) were incorrectly categorized as likely benign.¹¹
- *Impact on invasive procedures:* If used to make treatment decisions, the classifier would have resulted in fewer invasive diagnostic procedures being performed in those who were ultimately found to have benign nodules. In patients who underwent surgery, biopsy, or both, relative risk reduction rates were 29%, 43%, and 14%, respectively.¹¹

The investigators concluded that the integrated proteomic classifier appears to provide an opportunity to recategorize nodules and, thus, avoid unnecessary invasive follow-up.¹¹

Where to Go from Here?

Work from the American Thoracic Society and an ongoing clinical trial provide additional guidance on how biomarkers should be utilized in clinical care of pulmonary nodules.

ATS Policy Statement

The findings in these studies bode well in the quest to provide pulmonologists with biomarker tools that can better

identify benign nodules without needing invasive procedures. Presently, it is uncertain which biomarkers should be utilized (and when). To address this uncertainty, in 2017 the American Thoracic Society published a policy statement to guide clinicians and other decision-makers regarding what levels of evidence are required before particular molecular biomarkers are deemed appropriate for clinical practice.

The organization formed a steering committee, surveyed its members, developed key questions based on the answers, and formed the policy statement.¹² Among the key points addressed:

- Researchers should provide certain study results to help influence interpretation and clinical utility.
- The minimal accuracy of a biomarker should be determined via certain calculations to help justify investment in a clinical utility study.
- Use of a biomarker should help determine who will benefit most from screening, as well as who would be least likely to benefit.
- By definition, a clinically useful biomarker must, when compared with current standard of care, lead to 1) fewer lung cancer deaths in those tested without increasing harms or deaths; or 2) a similar number of lung cancer deaths with fewer harms and lower expense.
- A clinically useful biomarker can lead to appropriate therapy more quickly for patients with cancer and/or fewer inappropriate interventions in those with benign nodules.
- By definition, a clinically useful biomarker must lead to 1) earlier diagnosis of malignancies without a significant increase in procedures in patients with benign nodules; or 2) vice versa.
- Biomarker-stratified, enrichment, and biomarker strategy study designs should be used to determine if a biomarker is clinically useful.¹²

Watch the Spot Trial Update

Research is underway to help pulmonologists and patients decide how frequently to repeat CT scans to determine nodule growth.¹³ Watch the Spot is a multicenter, pragmatic, comparative-effectiveness trial with cluster randomization by hospital or health system that is comparing more and less intensive surveillance strategies in individuals with small pulmonary nodules. The trial is aiming to arrive at useful conclusions in part via:

- pragmatic integration of study procedures into existing clinical workflow;
- cluster randomization by hospital or health system;
- a system-level intervention for protocol-based care;
- technology-enabled methods to identify and passively enroll participants;
- data collection during routine clinical care; and
- linkage with state cancer registries to determine outcomes

Investigators are evaluating the percentage of malignant nodules that progress beyond stage T1a. They are also looking at patient-reported anxiety and emotional distress, nodule-related health care use, radiation exposure, and adherence. The trial is scheduled to be completed in February 2024.¹³

Conclusion

The increased detection of pulmonary nodules in the face of an inconsistent clinical evaluation presents significant challenges. Invasive testing for lower risk nodules is leading to unnecessary procedures. Conversely, there is also potential to undermanage malignant nodules, potentially delaying diagnosis. The emergence of biomarker tools offers pulmonologists the possibility of improving outcomes in patients with pulmonary nodules, avoiding unnecessary interventions and improving management with more precise targeting of patients who will benefit from increased management.

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Biomarker Use in Metastatic Non-Small Cell Lung Cancer: What the Pulmonologist Needs to Know

Introduction

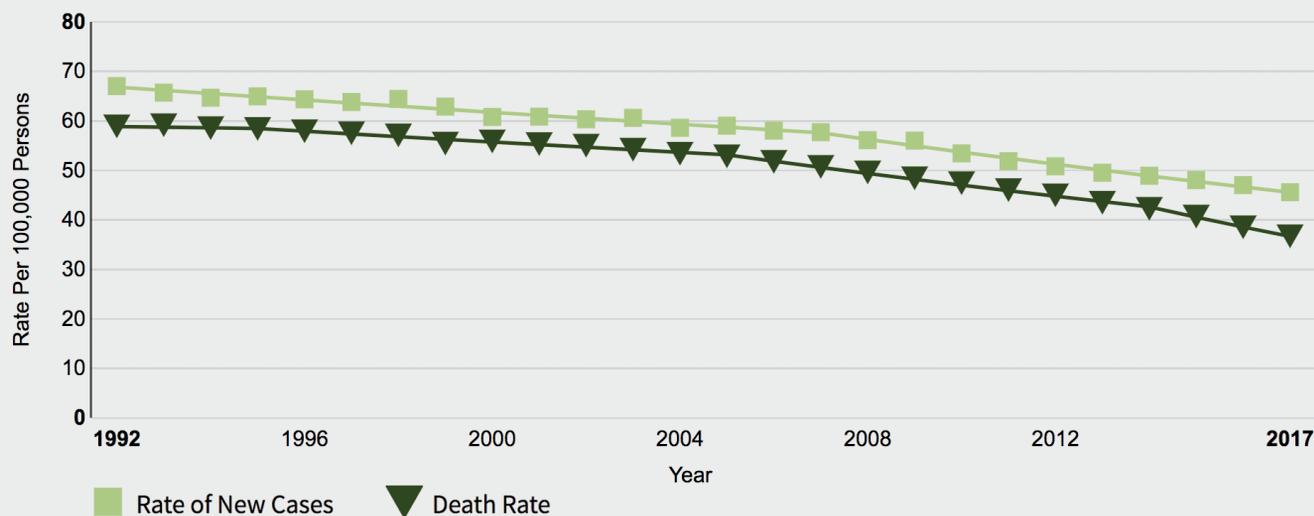
Lung cancer survival is steadily improving due to unprecedented advances in all aspects of lung cancer care (**Figure 1**).^{1,2} The emergence of *long-term lung cancer survivors* (ie, survival >5 years from diagnosis) and an anticipated 25% increase in the number of United States lung cancer survivors over the next decade³ underscore how recent diagnostic and treatment advances have improved lung cancer outcomes.⁴ Though lung cancer still causes more cancer-associated deaths than any other cancer type, improvements in lung cancer death rates are now outpacing breast and colon cancer.

One of the biggest challenges to continued improvement in lung cancer mortality is asymptomatic tumor growth, resulting in the abundance of patients being diagnosed with advanced stage (ie, metastatic) disease. Though tobacco cessation has had the single biggest influence on lung cancer mortality,⁵ systemic treatment options have shown the most benefit in patients with metastatic disease. In fact, today's targeted and immunotherapy treatment options have redefined lung cancer management and resulted in significant improvements in 1-year lung cancer survival.³ In stark contrast to lung cancer care 20 years prior, today's treatment decisions for systemic therapy in metastatic disease are made after deliberate and extensive biomarker testing. As members of the multi-

disciplinary lung cancer team who are frequently asked to obtain sufficient tissue for testing and staging, it is crucial that pulmonologists remain up-to-date with evidence- and guideline-based lung cancer evaluation and treatment. The goal of this review is to update pulmonologists on the "state" of biomarker testing in metastatic non-small cell lung cancer (NSCLC); we will review pivotal trials highlighting the importance of biomarker-driven therapy, review the current list of guideline-recommended biomarkers, and speculate on the future of biomarker testing in lung cancer.

In the last 20 years, tissue and blood biomarkers have been incorporated into lung cancer treatment guidelines for advanced stage NSCLC, including the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology (CAP/IASLC/AMP),⁶ National Comprehensive Cancer Network (NCCN),⁷ European Society for Medical Oncology (ESMO),⁸ and American Society of Clinical Oncology (ASCO).⁹ NCCN recommends testing include evaluation for Epidermal Growth Factor Receptor (*EGFR*) mutations, Anaplastic Lymphoma Kinase (*ALK*) rearrangement, ROS proto-oncogene 1 (*ROS1*) rearrangement, B-Raf proto-oncogene (*BRAF*) mutation, c-mesenchymal-epithelial transition factor (*c-MET*) mutations, rearranged during transfection (*RET*) rearrangements, and programmed death ligand 1 (PD-L1)

FIGURE 1: SEER lung cancer rates of death and new cases from 1992-2017



From National Cancer Institute Surveillance, Epidemiology, and End Results Program. Cancer stat facts: Lung and bronchus cancer. <https://seer.cancer.gov/statfacts/html/lungb.html>. Accessed May 28, 2020.

expression.⁷ Generally, broad-based molecular profiling is recommended (frequently via Next Generation Sequencing, NGS) for genetic testing and immunohistochemistry for PD-L1 testing. Several priorities from the guidelines should be recognized by pulmonologists¹⁰:

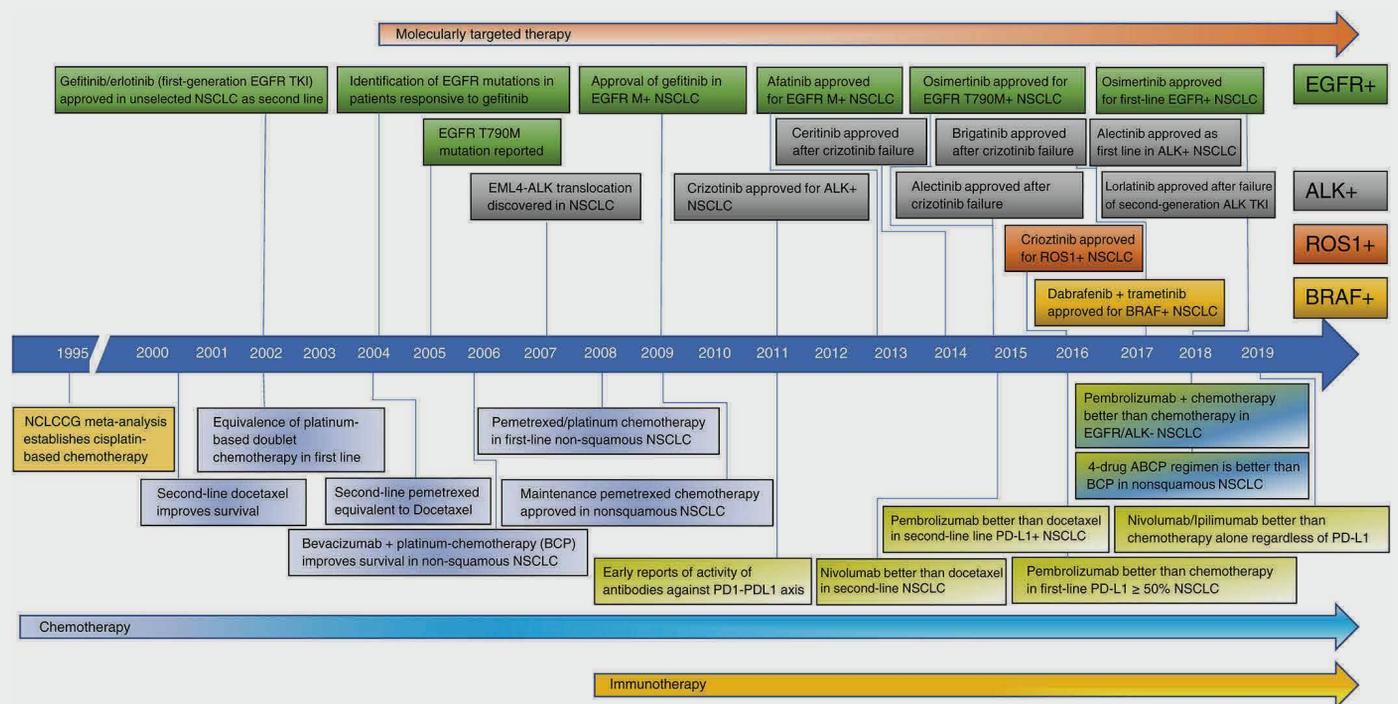
- Molecular biomarker testing is a necessary tool for determining the best treatment approach.
- Clinical guidelines can help clinicians determine which biomarkers and assays are most appropriate.
- Pulmonologists can best serve their patients who have advanced NSCLC by becoming familiar with the various tissue- and blood-based assays that have emerged.
- Next-generation sequencing reports require careful interpretation before treatment decisions are made.
- Plasma-based assays are noninvasive, rapid, and easy to repeat, whereas tissue-based assays tend to be more sensitive and, thus, can be used as a stand-alone test.
- Communication between pulmonologists, pathologists and oncologists is critical; and, development of care paths to facilitate adequate tissue acquisition, timely testing, and feedback will ensure that treatment decisions can be made quickly.

Despite a uniform recommendation to utilize biomarkers for treatment planning, adherence to biomarker testing in newly diagnosed metastatic NSCLC is inconsistent in the United States. For example, using claims data, rates of molecular

testing in metastatic NSCLC from 2015 to 2016 were estimated at 61%.¹¹ There are several barriers to consistent biomarker testing: lack of knowledge about the benefits of biomarker testing, resource availability (ie, tumor boards and sufficient laboratory testing), sufficient tumor tissue quantity and quality, cost, and reimbursement.¹⁰ Patients and physicians in community-based settings and outside the United States often face one or more of these barriers. It is our hope that this review clarifies the importance of consistent biomarker testing.

As mentioned above, systemic lung cancer treatments have expanded dramatically in recent years (**Figure 2**),¹² and biomarker testing is designed to identify those patients who are most likely to benefit from targeted agents, immunotherapy, chemotherapy, or a combination. As a reminder, targeted therapies are frequently tyrosine kinase inhibitors (TKIs). These drugs inhibit abnormal proteins that are the result of specific DNA mutations (eg, *EGFR* mutations). Immunotherapies (also known as immune checkpoint inhibitors) are monoclonal antibodies that inhibit the programmed cell death protein-1 (PD-1) receptor, PD-L1, or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), leading to increased antitumor activity by the body's immune system. We will begin with a summary of trial results involving targeted and immunotherapy agents that are improving outcomes in patients with advanced stage NSCLC. We will also review the increased clinical relevance of biomarkers,

FIGURE 2: Timeline of the development of systemic therapy in advanced NSCLC



Reprinted with permission from John Wiley & Sons, Inc. Ang MK, Mok TSK. Twenty-five years of respiratory: Advances in lung cancer. *Respirology*. 2020;25(1):26-31.

Abbreviations: ALK, anaplastic lymphoma kinase; NCLCCG, Non-small Cell Lung Cancer Collaborative Group; BRAF, B-Raf proto-oncogene, serine/threonine kinase; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD-1, programmed death protein-1; PD-L1, programmed death ligand 1; TKI, tyrosine kinase inhibitor.

preferred tissues for testing, tissue acquisition techniques, and future directions for biomarker testing.

Newer Agents and Improved Outcomes

A complete review of studies and approvals for targeted agents is beyond the scope of this article. Instead, we have selected several topics to demonstrate progression of biomarker testing and targeted treatments.

Targeted therapies in lung cancer were borne from the recognition that tumors with *EGFR* activating mutations responded to *EGFR* TKIs. First-generation *EGFR* therapies were approved (without the benefit of biomarker testing) in 2002, and Gefitinib (a first-generation TKI) was approved in 2009 for patients with *EGFR* mutations.¹² Trials in 2009 and 2010 showed improved progression-free survival (PFS) using Gefitinib (vs chemotherapy) in patients with *EGFR* mutations.^{13,14} In Maemondo and colleagues' multi-center phase 3 trial of 230 patients:

- Participants with metastatic NSCLC and *EGFR* mutations were randomized to either Gefitinib or standard chemotherapy. Gefitinib resulted in PFS rates that were twice that of chemotherapy, with median PFS 10.8 months in the Gefitinib group vs 5.4 months for those receiving chemotherapy. Those receiving the *EGFR* TKI were 70% less likely to experience death or disease progression.¹³

Subsequent to these studies, biomarker-based testing became standard of care.

Discovery of and therapies for *EGFR* mutations were followed by similar recognition of *ALK* rearrangements and targeting drugs. The *ALK* translocation was discovered in 2007, and therapy with Crizotinib in *ALK*+ patients was approved in 2011.¹² Crizotinib is another TKI and inhibits *ALK*. A 2011 analysis demonstrates efficacy of *ALK*-targeting therapy¹⁵:

- In a retrospective analysis of 438 individuals, Shaw and colleagues showed Crizotinib improved overall survival (OS) in patients with advanced, *ALK*-positive NSCLC. In the individuals who received Crizotinib during the phase 1 trial, median OS from the date of first dose had not been reached. One- and 2-year OS rates in these patients were 74% and 54%, respectively.

The histories of *ROS1*, *BRAF*, and the more recent Neurotrophic tyrosine receptor kinase (*NTRK*) mutation are similar, with biomarker recognition followed by improved outcomes using targeted therapies.

In addition to identifying targets for molecular therapies, biomarker-driven therapy has begun to identify oncologic mechanisms of resistance. For example, a Thr790Met (T790M) mutation was identified in *EGFR*+ patients who progressed on targeted therapy. The T790M mutation is now recognized as a mechanism of acquired resistance to *EGFR* therapy, and resistance can be overcome by Osimertinib, a third generation *EGFR* TKI.¹⁶ T790M testing is currently recommended for patients with *EGFR* mutations who have progressive disease on Erlotinib, Afatinib, Gefitinib, or Dacomitinib.

Much like the discovery of targeted therapies, immunotherapy has changed our paradigm for treatment in metastatic NSCLC. Though combination chemotherapy/immunotherapy

is now first-line treatment for most patients with metastatic NSCLC, the discovery of PD-L1 remains one of the most important biomarkers in NSCLC evaluation.

- In a phase 3 trial involving 305 individuals comparing Pembrolizumab (a PD-1 monoclonal antibody) and chemotherapy, immunotherapy significantly lengthened PFS and OS in patients with NSCLC and at least 50% PD-L1 tumor expression.¹⁷ At 6 months, the OS rate was 80% in the Pembrolizumab group.

Though subsequent studies have shown benefit of immunotherapy in many patients independent of PD-L1 testing, testing is still recommended since Pembrolizumab monotherapy is preferred for patients with $\geq 50\%$ PD-L1 expression.

Since the benefits of immunotherapy extend beyond PD-L1 testing, tumor mutational burden is an emerging biomarker that may predict benefit of combined immunotherapy¹⁸:

- In a phase 3 randomized trial involving 1104 individuals with NSCLC and high tumor mutational burden, combined Nivolumab (an anti-PD-1 antibody) and Ipilimumab (an anti CTLA-4 antibody) improved PFS compared with chemotherapy-alone, and benefit was noted independent of PD-L1 expression. Among participants with high tumor mutational burden, the 1-year PFS rate was 43% with Nivolumab plus Ipilimumab, compared with 13% for chemotherapy alone.

Biomarkers Gain Increased Clinical Relevance

As a result of the trials above showing improved survival compared to chemotherapy, a diagnosis of "non-small cell lung cancer" is no longer sufficient. In addition to staging and histological confirmation, biomarker testing is recommended for most NSCLCs. The NCCN recommends biomarker testing in all non-squamous NSCLC (ie, adenocarcinoma, large cell, and NSCLC not otherwise specified). Due to lower incidence of targeted mutations in squamous cell carcinoma (eg, *EGFR* mutations in <5% of these tumors), NCCN recommends that molecular testing should be considered in patients with squamous cell carcinomas who are never smokers, have small biopsy specimens, or have mixed histology.⁷ PD-L1 testing is recommended in both groups. As the number of targeted and immunotherapy agents has increased, so too has the list of biomarkers for testing. To ensure targetable biomarkers are not overlooked, broad-based molecular testing is recommended. For context, the complete list of available biomarkers is shown in **Table 1**. Presently, Kirsten ras oncogene (*KRAS*) mutation is the most common driver mutation and generally seen in former smokers.¹⁹ Though an agent is in testing,²⁰ unfortunately, *KRAS*-directed therapy is not currently available.

Due to a growing number of lung cancers with "actionable" biomarkers, improving survival, and favorable side effect profiles of newer therapies, lung cancer is now at the forefront of precision medicine (ie, treatment strategies personalized to individual variability).²¹ However, despite extensive molecular testing, most patients with lung cancer do not have "actionable" driver mutations. Notably, "actionable" mutations are more common in certain patient groups. For

example, *EGFR* mutations are common in non-smokers, women, and Asian patients.¹⁹ To clarify what portion of tumors have driver mutations, in 2009 the Lung Cancer Mutation Consortium (LCMC) was developed at 14 US-based sites.²² Over a 3-year period, LCMC tested lung adenocarcinomas for oncogenic driver mutations. LCMC evaluated tumors from 1007 patients for at least 1 gene and 733 of those patients for 10 genes. Investigators found an oncogenic driver in nearly two-thirds of those 733 individuals. They used the overall findings to direct approximately 30% of patients to targeted therapy or a clinical trial. Median survival in patients with an oncogenic driver and directed therapy was 3.5 years. This compared with 2.4 years in individuals with drivers who did not receive such therapy and 2.1 years in those without driver mutations. Investigators concluded that identifying biomarkers and targeting treatment in this way has redefined care for patients with lung cancer.

Tissue Acquisition: Timing and Preferred Testing Sources

The pulmonologist's role in the multi-disciplinary lung cancer team is multi-factorial, including diagnosis, staging, management of concomitant lung disease, smoking cessation, symptom control, and frequently, tissue acquisition utilizing minimally-invasive techniques. As the list of targetable mutations grows, acquisition of sufficient tissue has become increasingly important. In patients with advanced stage NSCLC, bronchoscopy, thoracentesis, and CT-guided biopsy are the most common procedural approaches. Guidelines from NCCN, American Thoracic Society, American College of Chest Physicians (CHEST), and American College of Radiology (ACR) are unified in stressing the importance of practices that promote collection of tissue samples sufficient for molecular testing. NCCN notes that the potential to obtain accurate test results for NSCLC could be diminished when employing minimally invasive specimen collection techniques, and it emphasizes the importance of obtaining enough tissue for all appropriate testing. In instances where minimal tissue is available, laboratories should implement dedicated history protocols and slide sectioning.⁷

Recommendations from NCCN, ACR, CHEST, and others acknowledge that timely *and* accurate tissue acquisition are imperative. Delays in therapy, overlooking a targetable mutation, or inaccurately staging a patient with metastatic lung cancer are examples where mistakes in tissue acquisition could lead to patient harm. In a 2009 analysis of 237 individuals with stage III NSCLC, investigators demonstrated that among patients who survived ≥ 5 years, risk of death was significantly higher in those who experienced delayed time to treatment.²³ To further emphasize the importance of timely tissue acquisition and accurate diagnosis, several reports have identified increased risk of severe treatment-related complications if immunotherapy precedes targeted therapy with Osimertinib. Since most patients with metastatic NSCLC will be eligible for combined chemotherapy/immunotherapy, it may be tempting to initiate these therapies while awaiting a molecular evaluation. However, an analysis published in 2019 showed that in individuals with *EGFR*-mutant NSCLC treated with PD-1 or PD-L1

TABLE 1: Biomarkers currently used in targeted therapy

Full Name	Abbreviation
Epidermal Growth Factor Receptor	EGFR
Anaplastic Lymphoma Kinase	ALK
ROS Proto-Oncogene 1, Receptor Tyrosine Kinase	ROS1
Neurotrophic Tyrosine Receptor Kinase	NTRK
Proto-Oncogene B-Raf-V600E	BRAF V600E
Mesenchymal-to-Epithelial Transition Exon 14 Skipping	METex14
Rearranged During Transfection	RET

blockade followed by Osimertinib, a small but substantial number of patients (15%) experienced at least 1 severe immune-related adverse event (frequently pneumonitis).²⁴ In summary, recent findings underscore the importance of ensuring complete testing and accurate diagnosis before initiating therapy.

Currently, tissue biopsy remains the standard for lung cancer diagnosis and molecular analysis, and pulmonologists are frequently called upon to perform bronchoscopy (including endobronchial ultrasound) for tissue acquisition and staging. Regarding procedure choice, the CHEST lung cancer guidelines recommend sampling the site of highest disease stage via the least invasive approach.²⁵ For example, sites of metastasis (eg, adrenal gland or lymph nodes) are preferred biopsy sites over primary lung tumors. With this approach, a patient's diagnosis and stage can be concurrently obtained with low risk of complication.

In addition to bronchoscopy, pleural fluid analysis can be used as an alternative to solid tissue. A malignant pleural effusion also establishes the disease as stage IVA. Further, the relative ease and low risk of thoracentesis make it an attractive alternative to procedures requiring conscious or deep sedation. In an analysis published in 2018, NGS was performed on 8 cell blocks of pleural effusions and 10 lung adenocarcinoma samples obtained by fine-needle aspiration. Investigators found that the pleural fluid samples produced better quality DNA than did formalin-fixed paraffin-embedded (FFPE) tissue or cell blocks. Meanwhile, DNA quality was similar when compared with FFPE cell blocks of pleural fluid samples. Thus, researchers concluded that fresh pleural fluid samples are a suitable alternative for molecular diagnostics.²⁶ Since the diagnostic yield of a single thoracentesis is only about 60% to 70% for a malignant pleural effusion, repeat sampling is recommended if the effusion re-accumulates.²⁵ In summary, thoracentesis is the test of choice in patients with NSCLC and an undiagnosed pleural effusion; separate tissue sampling should be pursued if the pleural fluid is negative x2 attempts.

In the last 5 years, liquid biopsy has become an option for patients with advanced NSCLC. This test uses blood sam-

ples to identify circulating tumor markers, primarily cell-free tumor DNA.²⁷ As a non-invasive mechanism of cancer diagnosis, liquid biopsy is an exciting potential advancement in lung cancer diagnosis. Presently, the yield of the test is low. As a result, clinical use is limited to the identification of driver mutations (eg, *EGFR* mutations) from circulating tumor DNA, especially when tissue biopsy specimens are insufficient or not safely obtainable.²⁸ As our recognition of biomarkers and circulating tumor DNA continue to improve, it seems likely that utilization of liquid biopsy will steadily increase.

Future Directions

We live in an exciting time for lung cancer management. Biomarkers have quickly taken a pivotal role in the evaluation of lung cancer patients with metastatic disease. Advances related to biomarker-guided therapies have placed lung cancer at the forefront of precision medicine. With the growing list of well-tolerated and efficacious systemic therapies, survival and quality of life for patients with metastatic NSCLC will almost certainly continue to improve. Moving forward, early reports of phase 1 testing of *KRAS*-directed therapies (the most frequently encountered mutation in patients with NSCLC) are yet *another* example of how biomarker-driven therapies are redefining how clinicians treat lung cancer.²⁰

In conclusion, lung cancer survival is steadily improving, and there are more treatment options for advanced stage NSCLC than ever. As therapies transition to oral delivery mechanisms and produce more long-term lung cancer survivors, the idea of lung cancer as a chronic and manageable disease seems within grasp. As clinicians and proceduralists for the lungs, it is imperative that pulmonologists remain aware of these precise diagnostics as well as biomarker-driven treatments options.

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