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NSCLC Management:

Advanced by Science, Challenged by Human Barriers

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Introduction

Gary H. is a 68-year-old man who presented to the hospital emergency department (ED) with chest pain. He had been forgoing routine medical exams over the last year due to the COVID-19 pandemic. Chest imaging showed signs of a lung mass and mediastinal adenopathy.

The ED clinician told Gary that he probably had advanced cancer – and that was all. Gary received no counseling or guidance on next steps but was referred to pulmonology. "Probably has advanced cancer" are the only words he heard from this clinician about his suspected disease.

Gary went to the referred pulmonary clinic for follow-up. There, he told the pulmonologist that his wife had died of lung cancer 8 years earlier. It was a rapid and traumatic experience, he recalled. She had undergone surgery but still required chemotherapy and radiation therapy for incomplete resection. Gary's wife lived less than 1 year after her diagnosis, a year marked by poor quality of life, treatment-related complications, depression, and anxiety. So, when the pulmonologist told him he probably had advanced lung cancer, he made up his mind. He said he did not wish to go through what his wife experienced. He did not want to be biopsied because he did not wish to be treated.

Gary's story is not uncommon among the roughly quarter of a million individuals diagnosed with lung cancer each year in the United States.[1] This commonality is a salient point for pulmonologists and other frontline clinicians, who may be the first point of contact for a new or suspected lung cancer diagnosis. It is not unusual to meet patients like Gary, who assume treatment to be a hellish experience followed by a rapid end. Their diminished expectations are based on outdated and often inaccurate depictions that come from greater society and, yes, from within the health care system itself.

For pulmonologists and other frontline clinicians, it is time to throw away the old playbook—the one that says survival is dismal, treatments are often harsh and difficult to tolerate, and patients should be advised to get their affairs in order. This playbook has allowed both clinician and patient to adopt respective mindsets that permit only a single course of action: refer to oncology and anticipate suffering to follow, with death shortly thereafter.

A new paradigm is evolving to replace this outdated playbook for lung cancer: early diagnosis through screening, more effective and more tolerable treatments, and survivorship. This shift highlights the vital position pulmonologists and other frontline clinicians now occupy in

offering screening to eligible patients, initiating appropriate diagnostic and staging procedures for patients with suspected lung cancer, and paving the way toward effective treatment and improved outcomes.

Still, significant barriers remain, including patient-, clinician-, and system-based barriers that prevent this paradigm from flourishing fully.

We will start with patients and their state of mind as they confront their new reality, because it is the patient's state of mind that will determine crucial first decisions about diagnosis and treatment.

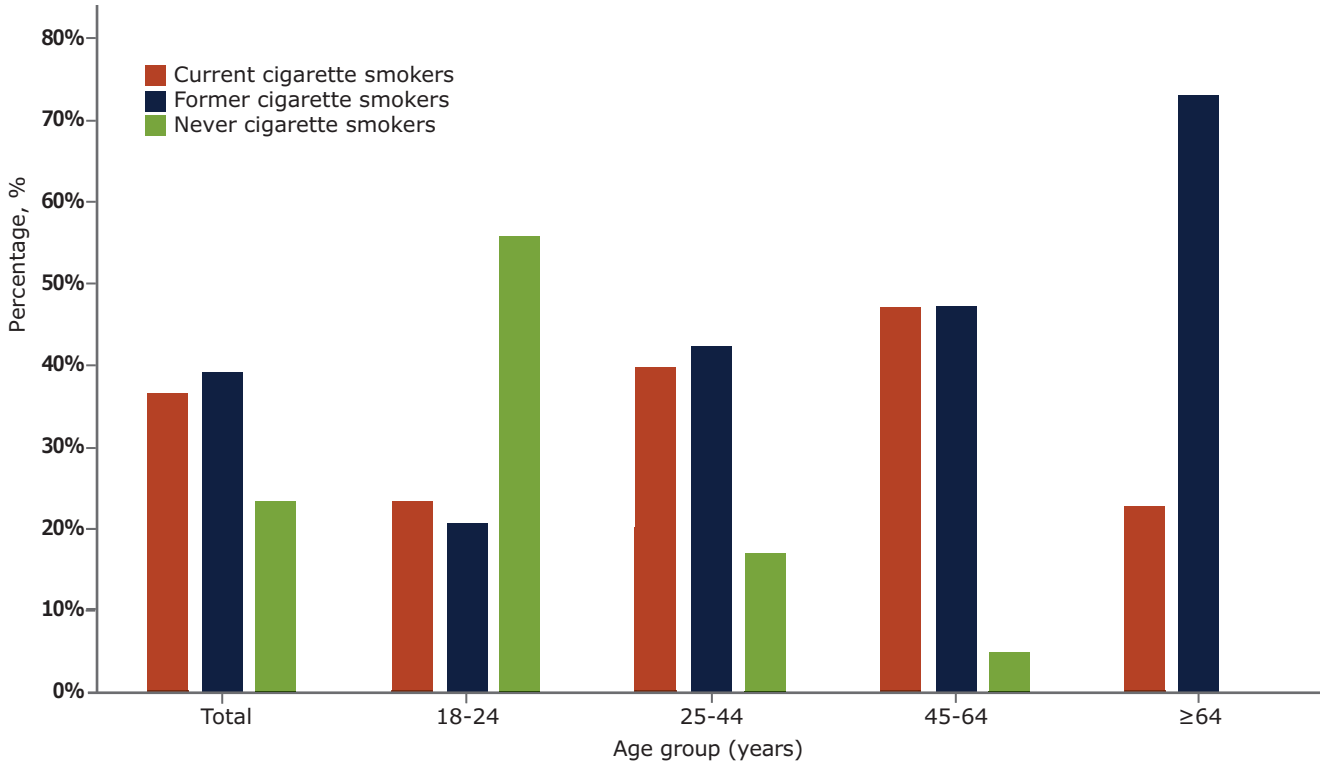
Today's Patients With Lung Cancer

It is worth reviewing the who, why, and how of lung cancer. Although more people have stopped smoking overall, cessation is not uniform across populations. Some groups continue to have higher levels of cigarette smoking, including Native Americans, Black Americans, individuals with mental health problems, individuals with lower educational attainment, and individuals identifying as lesbian, gay, bisexual, transgender, or queer (LGBTQ).[2,3]

Consider that in 2019, 14% of the US adult population smoked—yet 29% of Native Americans smoked commercial tobacco, as did 44% of adults with a general equivalency degree (GED) (vs 9% of those with an advanced degree). Thirty percent of the adult LGBTQ community smoked, compared with 5% of heterosexual adults. The figure is nearly double for people with a disability (26.9%), and triple for those with severe generalized anxiety disorder (45.3%).[2] The lure of e-cigarettes, especially among the young-adult cohort who have never smoked, is of concern: nearly 60% of those aged 18 to 24 years use e-cigarettes (**Figure 1**).

Lung cancer also occurs in individuals without a

FIGURE 1: Self-reported cigarette* and e-cigarette† use, by age group§ — National Health Interview Survey, United States, 2019[2]



Adapted from Cornelius ME, Wang TW, Jamal A, Loretan CG, Neff LJ. Tobacco Product Use Among Adults — United States, 2019. *MMWR Morb Mortal Wkly Rep.* 2020;69:1736–1742.

* Classification of study participants, per smoking status; Current smokers: Those who indicated that they had smoked ≥100 cigarettes in the past and continued smoking every day or on some days. Former smokers: Those who had smoked ≥100 cigarettes in the past but were "not at all" when interviewed. Never smokers: Those who hadn't smoked 100 cigarettes in their lifetime.

† Current e-cigarette users were defined as adults who reported e-cigarette use at least once during their lifetime and use "every day" or "some days" at the time of the interview.

§ The prevalence of never cigarette smokers among e-cigarette users aged 65 years and older is not presented because of relative standard error >30% or unweighted denominator <50.

history of cigarette smoking. Women experience a disproportionate burden of this type of cancer. Ten to 15% of lung cancer cases in Western countries are diagnosed in never smokers; the prevalence is even higher worldwide. Environmental exposures, genetic variations, hormonal factors, and secondhand smoke exposure have also been implicated. Radon, air pollution, household fumes, and infectious agents may be environmental contributors.[4]

Some genetic polymorphisms have been identified, in addition to an important somatic gene mutation; epidermal growth factor receptor (*EGFR*) is considered a biomarker for lung cancer, especially in never smokers (*discussed further on page 7 of this supplement*).[4]

Patient Barriers to Timely Diagnosis and Treatment

Research shows that people with lung cancer experience stigma that originates from a few sources: internalized stigma from the individuals themselves, actual or patient-perceived stigma from other individuals in the community, and actual or patient-perceived stigma from health care providers.

Fear and Denial

Focus groups involving individuals at risk for lung cancer show that denial can begin even before diagnosis. Fear and denial were shown to be barriers to seeking help; these were more prevalent in men.[5] A cohort study involving 379 individuals with newly diagnosed lung cancer showed that denial also plays a major role in delayed treatment; the average delay from symptom onset to contacting primary care was about 189 days. Denial was found to be one of the most significant factors causing delay.[6]

Internalized Stigma

Individuals diagnosed with lung cancer experience emotional states of regret, shame, and self-blame.[7,8]

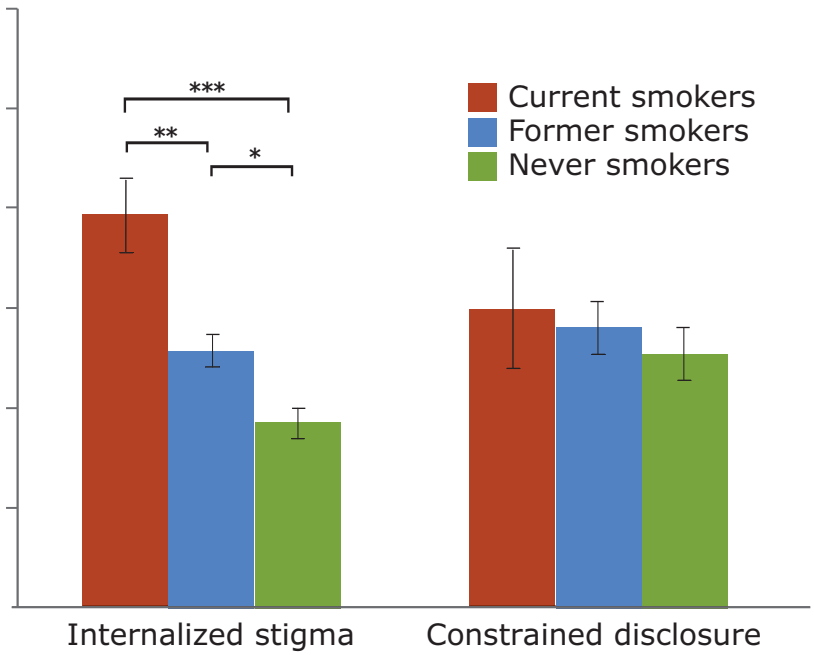
One study that included interviews and focus groups with patients with lung cancer discussed internalized stigma. Most feelings of self-blame were combined with guilt about the impact their diagnosis would have on their family.[8] Hamann and colleagues suggested that it is important to consider a patient's smoking history when assessing who may be more inclined to self-stigmatize.[7] Such stigmatization can lead to decreased well-being.

In a 12-week study of 101 adults undergoing lung cancer treatment, researchers found that, at baseline, individuals who currently or formerly smoked felt higher levels of internalized stigma compared with individuals who never smoked (**Figure 2**). Both internalized stigma and lack of disclosure (which did not significantly differ by smoking groups) were uniquely linked with poor emotional and physical well-being. Moreover, emotional and physical or functional well-being at entry was independent of factors such as demographics or smoking history. The authors also found that discomfort with disclosure and self-stigmatization should not necessarily be lumped together, as they noted that disclosure is linked with adverse psychological and physical well-being, both independent of self-stigmatization.[9]

External Stigma

In the Hamann analysis, most interviewees perceived stigma regardless of smoking status. Most said they were immediately asked by strangers or acquaintances about their smoking history, and many recounted how they felt devalued by family members, friends, and

FIGURE 2: Internalized stigma and constrained disclosure by smoking status[9]



Reprinted from *J Thorac Oncol*, 13(9), Williamson TJ, Choi AK, Kim JC, et al. A longitudinal investigation of internalized stigma, constrained disclosure, and quality of life across 12 weeks in lung cancer patients on active oncologic treatment, 1284-1293, © 2018, with permission from Elsevier.

Mean scores of internalized stigma and constrained disclosure by smoking status.
Note: *$p < .05$; **$p < .01$; ***$p < .001$; Error bars represent standard errors.

colleagues. One participant noted that although she never perceived or experienced stigma, she still felt she had to start any conversation about her disease by stating that she never smoked.[7]

A cross-sectional survey was administered in both 2008 and 2018 to oncologists, people with lung cancer, and members of the public. The 2018 analysis revealed that 60% of the public felt that people with lung cancer were partly to blame for their illness, similar to findings from the same analysis conducted 10 years earlier. It also appears that perceived stigma may be worsening. The individuals with lung cancer were also asked about stigma. In 2008, 31% said other people blamed them for their illness; in 2018, 52% answered the same way.[8] The following is a sampling of comments made by survey participants:

> *"When they'd say, 'What kind do you have,' and I'd say, 'Lung cancer,' they, even if it's somebody I don't know, say, 'Well, did you smoke?'"*
>
> *"But people that have lung cancer, it's kind of like, 'Well, you dumb a__, you shouldn't have been smoking. So you—you got what you deserved.'"*
>
> *"I mean, I think most people perceive that if you have lung cancer, you're kind of stupid, because you knew; you took risks when you smoked, so you—you're not very educated if you kept smoking. That compared to someone that gets brain cancer or some—whatever other kind of cancer that they might have, they don't feel like it's their fault."*

Clinician Barriers: Perceived and Otherwise

Although the physician's goal is to improve patient outcomes, inadvertent barriers to optimal patient care can exist here as well. An analysis by Wassenaar and colleagues looked at the role of clinicians in actual or perceived stigma. Nearly half of interviewees noted negativity from their providers, including smoking-related assumptions about individuals who did not smoke (or had never smoked).[10]

In a study published in 2007, 670 primary care clinicians were asked about their referral approach for individuals with local and metastatic disease. Half the clinicians were told their patients had breast cancer, and the other half, lung cancer. Clinicians were more likely to refer both early stage and metastatic cancer to medical oncology when they thought it was breast cancer rather than lung cancer. This study likely captured the reality of referral considering the relatively few number of of treatments. However, today's physicians who treat persons with metastatic lung cancer have treatment options that did not exist before, which should allow all patients the referral that they deserve.[8]

Frontline clinicians can reduce the contribution of denial to delay in care by screening eligible patients before symptoms occur and by thoroughly and compassionately evaluating their patients when symptoms develop.[11]

Systemic Barriers to Equitable Care

To illustrate the obstacles that patients face in receiving a timely diagnosis of lung cancer and quality treatment once diagnosed, consider the case of Michelle A., a 45-year-old woman who lives in the upper Midwest.

Michelle developed a persistent cough after a mild cold. After trying several over-the-counter treatments without resolution, she saw her primary care physician, who prescribed inhaled medications, oral steroids, oral antibiotics, and nasal steroids. Michelle found no relief. She had no major medical issues, never smoked cigarettes, and worked in offices without suspected exposure to asbestos. Michelle's mother, also from the upper Midwest, died of lung cancer in her late 50s. Despite this history, it was more than a year after symptoms started that Michelle was referred to a pulmonologist. She underwent a computed tomography (CT) of the chest, which demonstrated multiple bilateral ground glass and mixed solid opacities. A biopsy revealed lung adenocarcinoma.

Michelle's story is one that occurs time and again. In her case, gender and her nonsmoking history played a role in delayed diagnosis.

Others encounter socioeconomic, geographic, racial, and ethnic barriers that prevent timely treatment. Often, these barriers occur in tandem. Some of these barriers are unique to lung cancer and some impact health care access in general.

Gender and Geography

Lung cancer–related deaths began steadily declining in 1990 in the US population, but the trend was not seen among women until the mid-2000s, nor was it seen everywhere. As of 2015, some rural areas and states with low excise taxes on cigarettes and those that spent little on tobacco-control measures recorded an increase in death rates among women by as much as 13%.[12]

Location also has made a difference regarding standard of care. An analysis of the National Cancer Database showed that of the nearly 15,000 patients who underwent surgical resection for non-small cell lung cancer (NSCLC), 54% received guideline-endorsed, multiagent adjuvant chemotherapy. Patients less likely to receive

such treatment lived in rural areas, were uninsured, or were receiving Medicaid insurance.[13]

Race and Ethnicity

While surgery offers the best likelihood for cure for early-stage NSCLC, an analysis of the Surveillance, Epidemiology, and End Results Program database between 2004 and 2016 revealed that Black patients are diagnosed at more advanced stages and have lower rates of surgical resection for early-stage disease. While this finding had been reported previously, a recent study analyzed the impact of segregation on lung cancer care and found that residential segregation is associated with advanced stage at diagnosis and lower rates of surgical resection for early-stage disease in Black Americans.[14,15] This is just one example of how structural racism directly affects real patients.

When the US Preventive Services Task Force (USPSTF), in its latest guidance recommendation, lowered the age cutoff and decreased the number of pack-years to expand lung cancer screening eligibility and to reduce racial disparity, the numbers of those eligible did go up, but it remains to be seen what the real impact will be.

A survey to evaluate the impact of the revised USPSTF screening guidelines on racial and ethnic disparities showed that Black and Hispanic respondents were less likely to be screened under both the previous and revised recommendations. Black patients were more than 60% less likely than White patients to be screened under both previous and current guidelines, and Hispanic patients were 85% less likely to be screened under both guidelines.[16]

The task force reduced age and pack-years because Black patients develop lung cancer at an earlier age and at fewer pack-years of smoking. However, in one study including non-Hispanic Black patients, of the 501 patients who were eligible to be screened, only 19 were screened between 55 and 64 years old. The rest were screened when they reached Medicare-enrollment age. The authors noted that access to care likely determines if someone is screened.[17]

This is nothing new. Black and Hispanic patients have historically been screened for other cancers at a significantly lower frequency than White patients.[17] Barriers to access are deeply entrenched and must be overcome.

Lung Cancer Screening: The First Step Toward Optimizing Outcomes

Overcoming these barriers to improving lung cancer outcomes starts with the proper implementation of screening. Lung cancer screening has been recommended since 2013 for older individuals who have smoked, and annual low-dose chest CT has been shown to reduce lung cancer and overall mortality for older individuals who have a significant smoking history.[19] Benefit requires annual adherence to screening for patients who are willing and able to undergo curative treatment like surgical resection.

Yet lung cancer screening rates have been woefully low, especially compared with other cancers, such as breast and colon.[20,21] A population-based analysis of lung cancer screening rates among eligible adults as defined by the earlier task force guidelines showed that among 8.5 million of those eligible, just 6.6% and 6.5% underwent screening in 2019 and 2020, respectively.[22]

Screening is even low among US veterans, a contingent that is at high risk for lung cancer, though screening rates are rising. Between 2013 and 2017, the rates per 1000 eligible veterans at Veterans Affairs health systems nearly doubled each year, climbing from less than 1% to 27%. Despite these increases, the authors noted "a profound gap between recommended and delivered care."[23]

However, there is some positive news. One study that looked at lung cancer screening during the pandemic found that the national rate held steady as the COVID-19 pandemic settled in, and some states saw significant increases in screening rates between 2019 and 2020.[22]

Expanding Inclusion Criteria for Screening

The 2021 recommendation for screening is for adults aged 50 to 80 years with a 20 pack-year or more smoking history who either smoke or have quit within the last 15 years. The task force opted for simpler eligibility criteria compared to using a more comprehensive and complex risk calculation.[24]

The task force's new model for annual screening with low-dose CT expands inclusion by 87%. Compared with the 2013 recommendations, the new guidelines increase the relative percentage of eligible individuals by 112% for Hispanic people, 107% for Black people, and 78% for White people. Additionally, the relative percentage of eligible women increases by 96% and the percentage of eligible men by 80%.[24]

A modeling analysis suggests that compared with 2013 guidelines, these new criteria could:

- Avert 122 more deaths per 100,000 individuals
- Decrease the lung cancer mortality rate from 13% to 9.8%
- Increase life-years gained per 100,000 individuals, 45 to 90 years of age, over a lifetime of screening, from 4882 to 6918[24]

One drawback is that the new criteria could slightly increase the number of false-positive results per person screened over a lifetime of screening. The

estimated average number of false-positive results per screened individual ranged between 1.9 and 2.5 using the 2021 criteria vs 1.9 using the 2013 recommendations.[25]

Limiting False-Positive Results and Overdiagnosis

The American College of Radiology's Lung Imaging Reporting and Data System (Lung-RADS) is designed to limit false-positive screening results by separating negative and positive findings. The negative screening results are *negative* (category 1) and *benign negative* appearance (category 2), while the positive screening results are assigned to *probably benign* (category 3) and *suspicious* (category 4). Suspicious nodules are subcategorized as *probably suspicious,* with a 5% to 15% chance of malignancy (category 4A) or suspicious with a >15% chance of malignancy (categories 4B or 4X).[26]

Patients who receive a negative screening result (category 1) or benign-appearing nodules (category 2) are re-evaluated during their next annual screen. Those receiving a positive screening result are evaluated again prior to their next scheduled annual screen, ranging from follow-up CT at 6 months for patients with nodules that are probably benign (category 3) to positron emission tomography (PET), CT, or biopsy for certain suspicious nodules (categories 4A, 4B, or 4X).[26]

Use of the Lung-RADS criteria reduces the number of false-positive results compared with the National Lung Screening Trial (NLST) by raising the threshold for a positive finding. Using Lung-RADS, the false-positive result at baseline was 12.8% (vs 26.6% using the original NLST threshold for a positive finding). After baseline, the false-positive results were 5.3% and 21.8%, respectively.[26]

While the newest USPSTF screening recommendations would decrease the rate of overdiagnosis per positive screening (which ranged from 6.0% to 6.3% for 2021 vs 6.3% for 2013), it is important to note that the raw number of over-diagnosed cases would rise under the 2021 guidelines, from 83 to 94 per 100,000 individuals as compared with the 2013 guidelines of 69 per 100,000 individuals.[25] Therefore, judicious management of findings becomes even more crucial, favoring surveillance in nonaggressive lesions, rather than proceeding to biopsy or resection for all abnormalities.

Insurance Coverage Implications

The impact the new USPSTF lung cancer screening recommendations will have on insurance coverage, including Medicare and Medicaid, is still developing. The Affordable Care Act (ACA) requires private insurers to cover USPSTF recommendations graded A or B with no cost-sharing.[27]

The ACA authorizes Medicare to expand existing coverage to USPSTF recommendations graded A, B, C, or I. The Centers for Medicare and Medicaid Services recently endorsed the expanded eligibility criteria and reduced the barrier to shared decision making by removing the requirement for a licensed practitioner to conduct it face-to-face.[28] One criterion is that the patient must be asymptomatic. Medicaid coverage varies by state, but most states cover screening.

Lung Cancer Management: A New Paradigm for the Role of Pulmonologists

Patient stigma and fear, as well as systemic barriers, pose many challenges in pulmonologists' daily efforts to manage lung cancer, but over the last decade, many aids to diagnosis and staging have become available.

This raises the question: How do pulmonologists define their role today? That definition has changed with technological advancements and educational opportunities. Pulmonologists are probably involved in most of the lung cancer diagnoses in the United States, depending on local expertise and resources. Those who are lung cancer patient advocates and who exhibit best practices will establish the diagnosis (including a precise histologic classification), assess for molecular profiles, and oversee a complete staging assessment.

In the last 10 years, pulmonologists in general (not just interventional pulmonologists trained in accredited fellowships) have been introduced to new ways to diagnose and stage lung cancer. The Association of Bronchology and Interventional Pulmonology offers certification in advanced diagnostic bronchoscopy without fellowship training.[29] Now, bronchoscopy with endobronchial ultrasound (EBUS) and transbronchial needle aspiration (TBNA) are accepted as the standard of care for diagnosis and staging of mediastinal disease; most pulmonologists-in-training are learning this skill.[30] New bronchoscopy diagnostic technologies, such as guided bronchoscopy and robotic bronchoscopy, also permit improved access to peripheral lung lesions, which is important for obtaining diagnosis and staging in a single procedure.[31]

Diagnostic Advances

- Low-dose chest CT scan: Every patient with suspected lung cancer should undergo a CT scan of the chest, which can also help detect enlarged lymph nodes and help spot the spread of lung cancer to other areas of the body.[32]
- Bronchoscopy: Flexible bronchoscopy has a sensitivity of 88% for central airway lesions and overall sensitivity in the diagnosis of peripheral disease of between 36% and 88%, depending on the type of biopsy. Flexible bronchoscopy techniques such as

autofluorescence bronchoscopy and narrow-band imaging are highly sensitive for evaluating the central airway.[33]

- EBUS: EBUS and/or esophageal ultrasound are the preferred techniques for staging mediastinal nodal tissue associated with NSCLC. When CT imaging reveals a centrally located lung tumor next to the major airways, experts suggest using EBUS-guided fine-needle aspiration (EBUS-TBNA). In a meta-analysis comprising 14 studies involving 1175 individuals who underwent EBUS-TBNA for diagnosis of an intrapulmonary tumor, the diagnostic yield ranged between 0.72 and 0.96, with an average yield of 0.89. Sensitivity ranged from 0.77 to 0.97, with an average sensitivity rate of 0.91.[34]
- CT-guided transthoracic needle biopsy (TTNB): TTNB, widely used to obtain tissue from a peripheral lesion, has diagnostic accuracy ranging between 82% and 98%.[35] Percutaneous lung biopsy has an important role in lung cancer diagnosis, with high yield for peripheral lung lesions. However, TTNB has a higher rate of minor complications, including pneumothorax and hemorrhage, possibly increased in older individuals who smoke or have chronic obstructive pulmonary disease.[36] Percutaneous lung biopsy also does not offer a chance for simultaneous mediastinal staging, which is the standard of care in lung cancer.[35]

Distinguishing Cancer Types and Drivers

In 2015, the World Health Organization (WHO) modified the histopathologic classification of lung cancer to reflect the importance of understanding and identifying molecular profiles that can affect selection of an expanding array of treatment options and, ultimately, treatment outcomes.[37]

The 2 most common subtypes of NSCLC are adenocarcinoma, which comprises 60% of lung cancer types, and squamous cell carcinoma, which makes up 15%.[38] Distinguishing between adenocarcinoma and squamous cell carcinoma allows exploration of genetic alterations in lung adenocarcinoma that can now be treated with targeted therapies.

Histologic classification is important for other reasons, such as avoiding adverse reactions. For example, bevacizumab can cause higher rates of fatal or life-threatening hemoptysis in individuals with squamous cell carcinoma.[38]

Some distinctions:

- Adenocarcinoma in situ is preinvasive and has a lepidic pattern with a diameter of ≤3 cm (formerly called "bronchoalveolar carcinoma").[39]
- Minimally invasive adenocarcinoma (MIA) also has a diameter ≤3 cm, but an invasion size of ≤5 mm; without evidence of lymphovascular invasion, pleural invasion, or tumor necrosis.[39]
- Invasive adenocarcinoma can be further categorized as lepidic, papillary, acinar, micropapillary, or solid adenocarcinoma patterns.[39]

Squamous Cell Carcinoma Now Includes a Recategorized Variant

The 2015 WHO criteria categorize squamous cell carcinomas into keratinizing, nonkeratinizing, and basaloid variations. Basaloid had been categorized under large cell carcinoma, but then was shown to express squamous markers and was thus reclassified.[37] WHO notes that keratinizing tumors are those containing any amount of keratinization, whereas basaloid tumors contain >50% of the basaloid component regardless of keratinization status.[39] While there appears to be no clinical reason for subtyping squamous cell carcinoma of the lung, as new therapies emerge for this tumor, it may become clinically important to distinguish between the subtypes.[39] In 2021, WHO published an update on thoracic cancers that includes more emphasis on genetic testing, as compared with the 2015 classification, and information on small diagnostic sample classifications.[40]

Neuroendocrine Tumors Are a New Category

Invasive neuroendocrine tumors are divided into 3 subtypes: small-cell lung cancer, large-cell neuroendocrine tumors, and carcinoid tumors. Due to different disease prognosis and treatment, it is advisable to distinguish between high-grade neuroendocrine and carcinoid tumors. The former is an aggressive subtype that can occur in individuals with a history of heavy smoking, whereas the latter is typically indolent and usually occurs in those with no history of smoking.[37]

Tests to Lead to the Right Treatment

Molecular assays for NSCLC look for biomarkers, including gene mutations and alterations, to guide treatment decisions. Molecular alterations with currently available targeted therapies include:

- Epidermal growth factor receptor (*EGFR*) gene mutations
- Anaplastic lymphoma kinase (*ALK*) gene rearrangements
- ROS proto-oncogene receptor tyrosine kinase 1 (*ROS1*) rearrangements
- *BRAF* V600E mutations
- Mesenchymal-epithelial transition factor (*MET*)
- Rearranged during transfection (*RET*) gene
- Kirsten rat sarcoma (*KRAS*) mutation[38]

Timely Biomarker Testing

The increasing availability of targeted treatments underscores the need for early biomarker testing to determine optimal therapy. A recently published

cross-sectional study assessed pulmonologists' biomarker testing knowledge and use in practice. Among the 453 respondents, pulmonologists who used biomarker testing more frequently tended to have interventional training, practice in an academic setting, and were guided by institutional policy. Meanwhile, those who used biomarker testing less often were apt to be general pulmonologists in community practices with no institutional guidance (**Figure 3**).[41]

Individuals with newly diagnosed NSCLC often receive biomarker testing only after consultation with an oncologist—not at diagnosis—which prolongs testing and delays delivery of important information that can inform therapy. Clinicians in such settings could consider reflex-ordered testing for molecular biomarkers. One laboratory compared nonreflex to reflex testing to find gene alterations in lung adenocarcinoma samples. Mutations were detected in one-third of the samples submitted for nonreflex tests, with nearly twice that amount reported among the reflex tests. Turnaround time—defined as the number of days that passed from release of the initial surgical pathology report to release of the final molecular report—was also significantly reduced, from approximately 53 days using the nonreflex method in 2016 to approximately 16 days in 2018, 1 year after adoption of the reflex-ordered method.[42]

These advancements have led to more cooperation among pulmonologists, oncologists, and pathologists who are working together to ensure standard-of-care therapy without redundancy or excess cost.

The standard of care for detecting gene mutations and alterations in individuals with NSCLC involves testing tumor tissue. Next-generation sequencing of tumor tissue allows for comprehensive tests with a single assay.[38] Next-generation sequencing is substantially less expensive and significantly reduces waiting time compared with multiple single-gene tests when used in individuals covered by both Medicare and commercial insurance.[43]

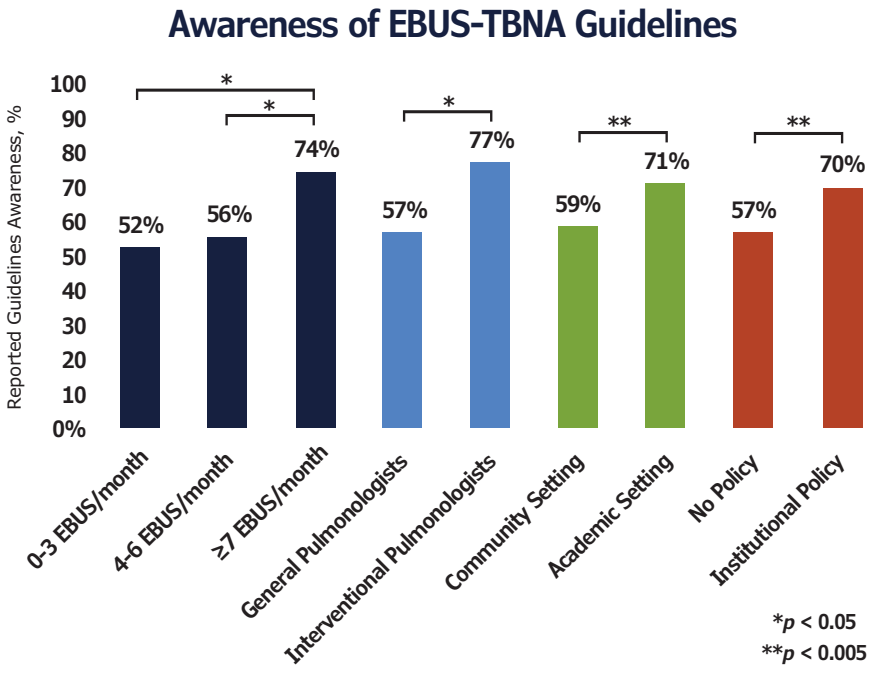
The Emergence of Liquid Biopsy

Besides testing tissue, clinicians now have the option of testing plasma-circulating tumor DNA (ctDNA), which can detect tumor DNA in the plasma. Some available testing platforms can identify more than three-fourths of the mutations found in tissue samples. Moreover, the observed plasma-derived mutations are the same as those seen in tissue in >95% of patients. Test results from ctDNA may be available more quickly when compared with tissue testing. However, just 1 in 5 individuals with a negative ctDNA test result has alterations that respond to drug treatment. Thus, combining ctDNA with tissue testing when feasible provides the best

FIGURE 3: Assessing extent of pulmonologists' knowledge and use of precision medicine[41]

EBUS-TBNA referral/performance associated with:
- Academic setting

Higher **biomarker testing rates** associated with:
- IP training
- Academic setting
- Presence of institutional policy



Adapted from *Chest*, 160(6), Fox AH, Jett JR, Roy UB, et al., Knowledge and practice patterns among pulmonologists for molecular biomarker testing in advanced non-small cell lung cancer, 2293-2303, © 2021, with permission from the American College of Chest Physicians.

guidance for treatment-responsive alterations.[38]

The technological advances that liquid biopsy provides prompted the International Association for the Study of Lung Cancer (IASLC) to produce a new consensus statement in 2021, updated from 2018. This new statement compares tissue biopsy with liquid biopsy, noting the advantages and disadvantages of each (**Table 1**).[44]

IASLC weighed these pros and cons and developed a proposed diagnostic algorithm to guide use of liquid biopsy in treatment-naïve advanced/metastatic NSCLC[44]:

- When a tissue sample is unavailable for tumor genotyping, IASLC recommends a "plasma-first approach" involving plasma ctDNA testing followed by a re-biopsy for tumor tissue testing if targetable drivers are not seen in plasma.
- When an adequate amount of tissue sample is available for tumor genotyping, IASLC recommends a "sequential approach" involving tumor tissue testing followed by ctDNA testing if tissue testing is incomplete.
- When tumor tissue is scant or thought to be of uncertain adequacy for genotyping, IASLC recommends a "complementary approach" involving concurrent tumor tissue and ctDNA testing.

Additional recommendations in the new IASLC consensus statement include[44]:

- Perform testing on a clinically validated, next-generation platform, not single-gene testing, to receive results that can be used with the increasing number of oncogene targets.
- Establish molecular tumor boards to help clinicians with treatment choices. This is becoming increasingly important with next-generation sequencing expected to soon become available in most places.

Determining PD-L1 Status

PD-L1 expression appears linked to increased tumor propagation and aggressiveness, as well as shorter survival times in individuals with NSCLC, particularly those with adenocarcinoma.[45]

Studies also show that using the PD-L1 immunohistochemical assay to develop a PD-L1 tumor proportion score can identify patients whose disease is likely to respond to immune checkpoint inhibitors (ICIs). Thus, testing tissue for the tumor proportion score in all individuals with metastatic NSCLC presents the opportunity for earlier intervention with a treatment that has a successful track record when confronting these aggressive tumors.[38]

As previously mentioned, reflex testing by pathologists of NSCLC reduces delay, especially when oncologists are not involved with the tissue acquisition. With clinical history and preprocedural imaging, pulmonologists may be in the best position to order next-generation sequencing and immunohistochemistries.[46]

Lung Cancer Staging

The attention to staging is crucial for the pulmonologist since it can involve technical aspects of the diagnostic procedure (such as performing biopsies of appropriate lymph nodes in the appropriate sequence). As stated earlier, correct staging determines appropriate treatment options and estimated prognosis.

The extent of disease in individuals with suspected or confirmed NSCLC has a direct impact on management and prognosis.[47] Indeed, the benefits of a precise histologic classification along with detailed and accurate biomarker testing are diminished if the patient's cancer is incorrectly staged.

Along with a general approach for testing suspected NSCLC, key staging recommendations from the American College of Chest Physicians (CHEST)

TABLE 1: Tissue and liquid biopsy advantages and disadvantages[44]

Tissue Biopsy

Advantages	Disadvantages
• Contains pathology information • Assesses DNA and non-DNA biomarkers • Assesses programmed death-ligand 1 (PD-L1) status	• Longer turnaround times • Limited tissue quantities • In progressive cases, re-biopsy may not be possible • Tumor heterogeneity

Liquid Biopsy

Advantages	Disadvantages
• Highly concordant • Rapid turnaround time • Minimally invasive • Repeatable • Improved capture of tumor heterogeneity and clonal evolution	• Non-DNA biomarkers cannot be evaluated • Increased cost if used along with tissue testing • False-negative results

guidelines on diagnosis and management of lung cancer are shown in **Tables 2A** and **2B**.[47] These guidelines will be updated later this year.

Recent Treatment Advances

This new paradigm for lung cancer management, as noted at the outset of this article, is rooted in rapid treatment advances that have taken place over the last decade or so. These developments are translating into the first improvements observed in lung cancer survival.[48]

Following is a summary of recent treatment advances:

- Thoracic surgery, surgical resection: Over the past 10 years, surgical resection rates have increased from 9% to 17% and surgeons are now more likely to perform the procedure on older individuals. The use of lung-sparing surgery is also on the rise, while the use of less-invasive video-assisted and robotically assisted surgery is enabling surgery to be performed with fewer complications.[48]
- Localized and stereotactic ablative radiotherapies: Stereotactic ablative radiotherapy (SABR) can precisely administer high doses of radiation to small lesions.

TABLE 2A: Extrathoracic staging of lung cancer[47]

Situation	Recommendation
Normal clinical evaluation and no suspicious extrathoracic irregularities on CT	Perform PET imaging (if available) to look for metastases Caveats: 1) Substitute bone scan and abdominal CT for PET imaging if necessary 2) PET is not required for: a. Ground glass opacities and an otherwise normal chest CT scan b. Individuals with peripheral clinical early-stage tumors

TABLE 2B: Mediastinal staging of lung cancer[47]

Situation	Recommendation
Extensive mediastinal intrusion but no distant metastases	CT imaging of the mediastinum appears sufficient
Discrete mediastinal lymph node enlargement and no distant metastases	Conduct invasive staging of the mediastinum
Activity in a mediastinal node is seen via PET but not CT, and there are no distant metastases	Conduct invasive staging of the mediastinum
N2 or N3 involvement is highly suspected, and there are no distant metastases	A needle technique is considered the best first test
N2 or N3 involvement is suspected as intermediate in those who have a central tumor and N1 node enlargement with no distant metastases	Conduct invasive staging of the mediastinum; a needle technique is considered the best first test
Peripheral stage 1A tumor	Invasive preoperative testing of the mediastinal nodes is unnecessary
Left upper lobe disease that requires invasive mediastinal staging	Conduct invasive assessment of the aortopulmonary window nodes if other nodes are found to be uninvolved

It is used primarily on individuals with early-stage disease who are not candidates for resection. Studies show the survival benefit as compared with traditional chest radiotherapy is 70% vs 53%. Research is being conducted to assess SABR's benefit in surgical candidates; so far, results are mixed.[48]

- Localized ablative therapies, including radiofrequency ablation: Radiofrequency ablation (RFA) is another option for early-stage, peripherally based small tumors or metastases. While there are no studies comparing RFA with surgical resection, a case series reports that 2-year overall survival is 75% in stage I inoperable lung cancer.[48]
- New systemic targeted therapies: These therapies target specific cell-signaling pathways and are indicated for individuals with specific tumor molecular profiles. They result in better outcomes with fewer serious side effects typically than traditional cytotoxic chemotherapy. US Food and Drug Administration (FDA)-approved targeted therapies are available to treat *EGFR, ALK, ROS-1, NTRK, BRAF* V600E, *KRAS*, *MET*, and *RET* genetic abnormalities.[49]
- ICIs: First approved for lung cancer in 2014, ICIs harness the power of the immune system to treat cancer, rather than relying on cytotoxic chemotherapy. Rather than allowing cancer cells to go undetected by T cells, ICIs restore T-cell antitumor activity.[50] Six immuno-oncology agents (PD-1/PD-L1/CLTA-4 inhibitors) are currently approved for lung cancer treatment. They are pembrolizumab (Merck & Co), nivolumab (Bristol Myers Squibb), atezolizumab (Roche), durvalumab (AstraZeneca), cemiplimab (Regeneron), and ipilimumab (Bristol Myers Squibb).
- ICIs have been approved as first-line therapy for metastatic disease, maintenance therapy after conventional concurrent chemoradiotherapy, and, most recently, adjuvant therapy for stages II and IIIa disease after surgery and chemotherapy in patients with PD-L1–expressing tumors.[51-54]

Supportive and Palliative Care

Pulmonologists also can play a supportive role in advanced lung cancer. Supportive care includes interventional bronchoscopy and pleural procedures. An analysis using the AQuIRE Bronchoscopy Registry evaluated therapeutic procedures in 947 individuals. Technical success rates were realized in 93% of procedures, and nearly half of the patients experienced significant relief from dyspnea and improved quality of life.[55]

- Localized and stereotactic ablative radiotherapies: Malignant pleural effusions can be managed with palliative interventional procedures, including thoracentesis, chest tube drainage with chemical pleurodesis (shown to have a 50% to 95% success rate), surgical pleurodesis for those fit for surgery (75% to 100% success rate), or placement of pleural drain catheter (85% to 95% success rate).[56]

Central Airway Obstruction

Caused by endobronchial tumor growth or extrinsic tumor compression, central airway obstruction can lead to dyspnea, postobstructive pneumonia, hemoptysis, or respiratory failure. One-third or more of patients with NSCLC present with central airway involvement at some point in their disease. Interventional pulmonologists can use mechanical debulking, thermal ablation (eg, laser, electrocautery, argon plasma coagulation), cryosurgery, and/or stenting to relieve central airway obstruction.[57]

Specialist palliative care support plays an important role in lung cancer care. In a study involving ambulatory individuals with metastatic NSCLC, patients who received early specialist palliative care experienced many benefits compared to those who underwent standard of care, including better median survival, better quality of life scores, and fewer symptoms of depression. They were also less likely to receive aggressive end-of-life care support. Integrating supportive care into standard oncology care for individuals with advanced disease is recommended by the American Society of Clinical Oncology (ASCO), which also found after reviewing clinical trials that patients have an improved quality of life, decreased depression, and improved care satisfaction.[48]

Precision Cancer Treatment: Thoracic Complications and Adverse Events

As the treatment paradigm shifts, so should the pulmonologist's awareness of potential pulmonary-related adverse events that can accompany use of targeted therapies and ICIs. Pulmonologists should be prepared to help manage pneumonitis and sarcoid-like granulomatosis, which have been observed with use of certain targeted treatments and ICIs.[58]

Adverse effects of ICIs can impact any organ system, but pneumonitis is more common in patients undergoing lung cancer treatment, occurring in approximately 5% of patients with lung cancer who are treated with an ICI. ASCO has published guidelines for managing these immune-related adverse events.[59]

Pneumonitis

Sometimes referred to as checkpoint inhibitor pneumonitis, the condition is usually mild but may require permanent drug discontinuation and/or other systemic anti-inflammatory therapy. Median onset is approximately 10 weeks after starting treatment. Symptoms are primarily dyspnea and cough, but also can include fever and chest pain. Milder cases present with asymptomatic chest imaging abnormalities, usually

seen on surveillance imaging. Management of the condition depends on severity (**Table 3**). Individuals with more severe involvement (eg, need for oxygen, hospitalization, or >50% of lung parenchyma involved) may be referred for evaluation and management by pulmonologists. Bronchoscopy with bronchoalveolar lavage may be indicated to rule out infection or other causes, as presentation can vary. Management is similar to that for cryptogenic organizing pneumonia: prednisone 1 to 2 mg/kg/d or methylprednisolone given intravenously at 1 to 2 mg/kg/d. Corticosteroids should be tapered over the course of at least 4 to 6 weeks.[53]

Sarcoid-like Granulomatosis

Note that the prevalence of this condition may be underestimated.[59] Sarcoid-like granulomatosis can occur with or without new or enlarging lymphadenopathy; it is important to recognize the condition as an immunologic reaction and not as disease progression. EBUS-TBNA is needed to secure this diagnosis in patients with enlarging mediastinal adenopathy.[60] Bronchoalveolar lavage may demonstrate lymphocytic interstitial alveolitis.[59] As with sarcoidosis, treatment is indicated only in the presence of physiologic dysfunction.

Pulmonary Hemorrhage, Pulmonary Embolism, and Pneumothorax

Pulmonary hemorrhage, pulmonary embolism, and pneumothorax have been observed with use of certain targeted treatments in individuals with lung cancer. Pulmonary hemorrhage can range from minor mucocutaneous hemorrhage to major hemoptysis. Pulmonary embolism is known to be a major complication in patients with lung cancer and is linked with treatment

TABLE 3: Management of checkpoint inhibitor pneumonitis[53]

Grade	Guideline for Management

G1
 	
No symptom
 	
Limited to a single lobe or <25% lung parenchyma
	• Consider holding ICIs; monitor symptoms every 2 to 3 days
	• May offer 1 repeat CT in 3 to 4 weeks
	• In patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3 to 4 weeks
	  ◦ If improvement is observed, continue to follow up
	  ◦ If condition worsens, treat as G2 or G3 to G4

G2
 	
New symptoms or worsening symptoms, including shortness of breath, cough, chest pain, fever, and anoxia
 	
Involves multiple lung lobes and reaches 25–50% of lung parenchyma, affecting daily life, requiring drug intervention
	• Hold ICIs until resolution to G1 or less
	• Consider infectious workup: nasal swab for potential viral pathogens sputum culture, blood culture, and urine culture
	• Consider chest CT with contrast; repeat chest CT in 3 to 4 weeks
	• Consider empiric antibiotics if infection has not yet been fully excluded
	• Prednisone IV 1 to 2 mg/kg/d
	  ◦ If improvement is observed, start slow steroid taper by 5 to 10 mg/week over 4 to 6 weeks
	  ◦ If condition worsens, treat as G3 to G4

G3/G4
 	
G3: Serious new complications
 	
Involves all lung lobes or >50% of lung parenchyma, limited personal self-care ability, requiring oxygen inhalation and hospitalization
 	
G4: Life-threatening dyspnea, acute respiratory distress syndrome requiring urgent intervention such as intubation
	• Permanently discontinue ICIs
	• Pulmonary consultation for bronchoscopy with bronchoalveolar lavage
	• Consider biopsies for atypical lesions; methylprednisolone IV 2 to 4 mg/kg/d
	  ◦ If improvement is observed, taper corticosteroids over 4 to 6 weeks
	  ◦ If no improvement or situation worsens after 48 h: add infliximab IV 5 mg/kg
	  • or MMF IV 1 g BID
	  • or IVIG for 5 days
	  • or cyclophosphamide

Adapted from Zhu S, Fu Y, Zhu B, Zhang B, Wang J. Pneumonitis induced by immune checkpoint inhibitors: From clinical data to translational investigation. *Front Oncol*. 2020;10:1785.

Abbreviations: ICIs, immune checkpoint inhibitors; CT, computed tomography; DLCO, diffusing capacity of lungs for carbon monoxide; IV, intravenous; MMF, mycophenolate mofetil; BID, 2 times daily; and IVIG, intravenous immunoglobulin.

involving vascular endothelial growth factor inhibitors. Pneumothorax is rare but known to occur.[55]

Summary

A new paradigm is developing for managing lung cancer as the disease is being diagnosed earlier, myriad new treatments are proving to be more effective and better tolerated, and patients are living longer and with better life quality. However, significant barriers remain, including stigma, denial, socioeconomic impediments, racial and ethnic disparities, and low levels of lung cancer screening. New screening recommendations from the USPSTF expand the potential screening population by lowering the age for initiating screening from 55 to 50 and reducing the pack-year history threshold from 30 to 20. The new guidelines may also help address racial, ethnic, and gender disparities.

Pulmonologists are playing an ever-increasing role in diagnosing and staging lung cancer. More are being certified in advanced diagnostic bronchoscopy, and accrediting fellowships have been established. A vast array of precision therapy options is now available. Which one is selected is hugely dependent on the work pulmonologists do when diagnosing lung cancer, including histologic classification, molecular testing, determining tumor proportion score, and staging.

The promise that these therapies offer can be tempered with associated toxicities, issues that a pulmonologist may be asked to help manage. These adverse events include pneumonitis, sarcoid-like granulomatosis, pulmonary hemorrhage, pulmonary embolism, and pneumothorax.

Finally, consider these best-practice recommendations for optimal management of patients with lung cancer:

1. If the primary care clinicians you work with have different referral criteria for different kinds of advanced cancers, consider asking them why, given the shifting lung cancer management strategies.
2. Expanded criteria have nearly doubled the population that is eligible for screening, so room for improvement exists with all health care entities that conduct these tests. A conversation with community stakeholders to adopt best practices for your patients could be in order.
3. Ensure that primary care clinicians you work with in practice or via referral are aware of the new lower age and smoking history thresholds at which lung cancer screening should start.
4. Consider how the new task force screening recommendations impact private and government insurance, as younger individuals may now be candidates for screening with no cost or cost-sharing.
5. If feasible, work with diagnostic laboratories that use reflex-ordered testing for molecular biomarkers. This strategy can increase variant detection rates and improve turnaround time.
6. Liquid biopsy is emerging quickly as a diagnostic option. It has numerous advantages and disadvantages and requires tailored approaches.
7. The diagnostic laboratories you use should test tissue for the tumor proportion score in all individuals with metastatic NSCLC.
8. Checkpoint inhibitor pneumonitis is common and may need management by pulmonologists, as individuals with severe pneumonitis or sarcoid-like granulomatosis may be referred to you for diagnosis, treatment, or both.
9. Patients with lung cancer face emotional and physical distress; they are deserving of management assistance from a pulmonologist.

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