Received: 9 December 2021 | Revised: 5 March 2022 | Accepted: 5 April 2022

DOI: 10.1002/cncr.34628

POSITION STATEMENT

The American Cancer Society National Lung Cancer Roundtable strategic plan: Advancing comprehensive biomarker testing in non–small cell lung cancer

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Funding information

The American Cancer Society National Lung Cancer Roundtable; National Cancer Institute/National Institutes of Health, Grant/Award Number: K12 CA157688; The Alice and

Abstract

Comprehensive biomarker testing is a crucial requirement for the optimal treatment of advanced-stage non–small cell lung cancer (NSCLC), with emerging relevance in the adjuvant treatment setting. To advance its goal of ensuring optimal therapy for persons diagnosed with lung cancer, the American Cancer Society National Lung Cancer Roundtable (ACS NLCRT) held *The Summit on Optimizing Lung Cancer Biomarkers in Practice* in September 2020 to align its partners toward the goal of ensuring comprehensive biomarker testing for all eligible patients with NSCLC. The ACS NLCRT's Strategic Plan for Advancing Comprehensive Biomarker Testing in NSCLC, a product of the summit, comprises actions to promote comprehensive biomarker testing for all eligible patients. The approach is multifaceted, including policy-level advocacy and the development and dissemination of targeted educational materials, clinical decision tools, and guides to patients, physicians, and payers aimed at ameliorating barriers to testing experienced by each of these groups.

Plain language summary

- The ACS NLCRT works to improve care for patients with lung cancer.
- The ACS NLCRT supports comprehensive biomarker testing as essential to determine treatment options for all eligible patients with non–small cell lung cancer.
- Many factors lead to some patients not receiving optimal biomarker testing.
- The ACS NLCRT held a collaborative summit and developed a strategic plan to achieve and promote comprehensive biomarker testing for all patients.

Stephen D. Cutler Fund; the Satherlie Family Research Fund

- These plans include developing educational materials and physician tools and advocating for national policies in support of biomarker testing.

KEYWORDS
biomarker testing, health services, immunotherapies, lung cancer, molecular-targeted therapies, personalized medicine

BACKGROUND

Targeted therapy and immunotherapy are altering the treatment landscape of non–small cell lung cancer (NSCLC). Their use is guided by the biomarker profile of each patient's cancer. Although historically limited to patients with stage IV NSCLC, the landscape is rapidly changing such that patients with surgically resected stage IB or higher disease are now candidates for biomarker testing that can inform decisions on adjuvant therapy.[1] Assessing NSCLC for oncogenic driver mutations and immune inhibitory protein expression to determine patients' eligibility for these therapies is optimally performed during the diagnostic and staging procedures before treatment initiation. Patients with NSCLC who have actionable biomarkers and are treated with targeted therapies have longer survival and improved health-related quality of life compared with patients who receive conventional therapies.[2,3]

Despite the potential benefits of targeted therapy and immunotherapy, evidence exists that biomarker testing is underused and often not comprehensive. Although rates of testing are increasing as awareness of its value increases among physicians and institutions, testing rates remain much lower than optimal, and testing strategies for individual actionable biomarkers vary.[4–6] Evidence shows testing rates for *EGFR* mutations and *ALK* rearrangements, which have had approved targeted therapies the longest, are >80%, whereas other biomarkers more recently linked to specific therapies are tested at much lower rates. One study examined seven cancer programs over 3 months in 2017 and demonstrated testing rates of 95% for *EGFR*, 94% for *ALK*, but only 88% for *ROS1*, and 57% for PD-L1 among patients with metastatic nonsquamous NSCLC.[7] A 2018 survey demonstrated a similar pattern, with higher testing rates for *EGFR*, *ALK*, and *ROS1* mutations (range, 79%–99%) but lower rates of testing for *BRAF*, *KRAS*, *MET*, *RET*, and *HER2/ERBB2*, mutations (range, 5%–73%).[8] In a review of a community-based oncology network from 2013 to 2015, 59% of patients with stage IIIB or greater, nonsquamous NSCLC were tested for both *EGFR* and *ALK* mutations, and only 8% were tested for all mutations that were recommended by the National Comprehensive Cancer Network (NCCN) at the time of the study.[9] Variable and noncomprehensive biomarker testing patterns are just one indicator of the inadequate implementation of personalized medicine in NSCLC.

The joint guideline statement by the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association of Molecular Pathologists (AMP), as well as the NCCN guidelines, provide detailed guidance for testing specific biomarkers.[10,11] These guidelines also support broad panel testing, which is capable of assessing all actionable driver mutations and additional mutations, including those that do not currently have associated approved therapies but are likely to have effective treatments within the lifetimes of some patients. The primary benefit of testing that extends beyond actionable biomarkers is to facilitate selection into clinical trials.[12,13] For the purpose of the current article, *comprehensive biomarker testing* refers to a process that, at a minimum, assesses for all possible guideline-recommended and actionable biomarkers for a patient's lung cancer subtype.

Comprehensive biomarker testing is important because it drives eligibility for targeted therapy and immunotherapy. For example, first-line treatment with osimertinib and alectinib is associated with median survivals greater than 3 and 5 years for patients with advanced NSCLC who have *EGFR* mutations and *ALK* rearrangements, respectively.[14,15] By comparison, older clinical trials of first-line treatment with pemetrexed and cisplatin exhibited a median survival in unselected patients with NSCLC <1 year.[16]

The American Cancer Society National Lung Cancer Roundtable (ACS NLCRT) was established in 2016 to lessen the impact of lung cancer through prevention, early detection, optimal diagnosis, and treatment in the United States and around the world. It is a national coalition of organizations and invited individuals representative of the entire lung cancer community. The Triage for Appropriate Treatment Task Group of the ACS NLCRT held *The Summit on Optimizing Lung Cancer Biomarkers in Practice* (the Biomarker Summit) to align members and improve biomarker testing. The stated mission is to ensure all eligible patients receive comprehensive biomarker testing to identify the most effective treatments available. This report serves as a summary of the ACS NLCRT's Strategic Plan for Advancing Biomarker Testing to promote comprehensive biomarker testing for all eligible patients with lung cancer.

METHODS

Background for the Biomarker Summit

The Biomarker Summit, an inaugural 2-day virtual meeting convened by the ACS NLCRT in September 2020, involved more than 85 participants from 75 member organizations. The theme was *Access to High-Quality Biomarker Testing for All Eligible Patients With NSCLC: No Patient*

Left Behind! The diverse group of participants included clinicians (with backgrounds in primary care, medical oncology, thoracic surgery, pulmonology, radiology, and pathology), patient advocates, researchers, public health professionals, and representatives of pharmaceutical and diagnostic companies, government agencies, and health plan providers.

The Biomarker Summit

The Biomarker Summit's activities were focused on five key challenges to universal comprehensive biomarker testing identified by the ACS NLCRT Steering Committee (Table 1). The agenda included: (1) six expert presentations on the current state of biomarker testing and each of the five key challenges; (2) sharing of experiences from patient advocates; (3) a series of *confessionals* from representatives of groups essential to the process of biomarker testing (primary care providers, proceduralists, oncologists, pathologists, and payers), the purpose of which was to promote open sharing of information on how practices of these groups contribute to barriers to comprehensive biomarker testing in their unique role; (4) small group sessions were charged with developing strategies to address barriers identified in the presentations and confessionals and then sharing them with the larger group; and (5) a panel discussion with representatives of advocacy groups, industry, and payer organizations that explored perceived and real barriers to comprehensive biomarker testing.

Members of the ACS NLCRT Triage for Appropriate Treatment Task Group outlined and prioritized the key information, perspectives, and strategies from the Biomarker Summit. A writing group composed of Task Group members developed an article that was reviewed and revised before submission.

RESULTS

Based on presentations and discussions during the Biomarker Summit, the ACS NLCRT Steering Committee developed the NLCRT's Strategic Plan for Advancing Biomarker Testing (Table 2), which aims to address access barriers to comprehensive biomarker testing (Table 1). These strategies and initiatives were delegated to appropriate ACS NLCRT committees and subcommittees for further planning and enactment.

The five key challenges to comprehensive biomarker testing identified by the Triage for Appropriate Treatment Task Group represent heavily interconnected barriers that span across the purview of multiple medical subspecialties and require sustained interdisciplinary communication and teamwork. Multidisciplinary collaboration has established benefits in oncologic care, and the ACS NLCRT considers a collaborative approach essential in this initiative.[17–19] For instance, oncologists working to reduce turnaround time must engage pathologists about the biomarker platform and proceduralists about the amount of tissue needed for the chosen assay. Furthermore, there is need for consensus on the most appropriate specialist(s) responsible for requesting and ordering testing. Although oncologists are typically responsible for acting on results, ideally the results should be available by the first oncology appointment to facilitate treatment decisions. Therefore, coordination among physicians within an institution to determine the workflow for biomarker testing is an important step to achieve timely universal testing. In addition, different groups and subspecialties contribute to the barriers for timely completion of comprehensive biomarker testing during the multistep process that newly diagnosed patients undergo (Figure 1). Interdisciplinary communication and collaboration are essential to achieve comprehensive biomarker testing for all eligible patients and are essential to each component of the ACS NLCRT's strategic plan.

Key challenge 1: Knowledge gaps surrounding indications and value of comprehensive biomarker testing

Inconsistent terminology describing comprehensive biomarker testing is one obstacle shared by both patients and physicians. The ACS NLCRT Steering Committee identified more than 22 terms used

TABLE 1 Five key challenge areas and recommendations for achieving comprehensive biomarker testing

Five key challenge areas	Recommendations
Challenge 1. Knowledge gaps regarding the value and indications for testing	Recommendation 1. Disseminate clear and consistent educational materials for biomarker testing to physicians and patients.
Challenge 2. Procuring adequate tissue for evaluation	Recommendation 2. Provide education to proceduralists performing tissue sampling for potential lung cancer and guide the development of institutional policies promoting adequate tissue collection.
Challenge 3. Choice of assay and turnaround time	Recommendation 3. Promote the use of guideline-driven biomarker panel testing through testing algorithms and implementation of reflex testing.
Challenge 4. Accurate interpretation and communication of testing results	Recommendation 4. Encourage standardized biomarker test reports and develop algorithms that aid in directing treatment.
Challenge 5. Reimbursement, cost, and coverage	Recommendation 5. Remove the disconnect between payer policies and evidence-based guidelines for comprehensive biomarker testing to increase coverage and avoid delays.

TABLE 2 American Cancer Society National Lung Cancer Roundtable strategic plan for advancing comprehensive biomarker testing in non–small cell lung cancer

Educate

- Develop educational materials with uniform content, messaging, and terminology, and update regularly.
- Prepare a white paper defining comprehensive biomarker testing with standard definitions and language.

Disseminate

- Identify ways to disseminate information across subspecialties in both academic and nonacademic settings and to all patients, including those in underserved communities.
- Partner with professional organizations to disseminate information at national, local, state, and regional meetings as well as through ongoing webinars and other online venues.

Assess/provide feedback

- Develop benchmark performance metrics and assessment tools for evaluating performance in health care organizations.
- Establish a platform for biomarker testing performance feedback for individual providers.

Optimize/standardize

- Develop a playbook to standardize and optimize workflows for every step of the biomarker testing process (from ordering the test through reimbursement).
- Provide algorithms for preauthorization of biomarker testing for third-party payers.
- Provide a guide for standardized evidence for third-party coverage decisions.

Advocate/legislate

- Advocate for dual comprehensive blood and tissue biomarker testing.
- Partner with professional organizations to generate uniform practice guidelines.
- Implement public policy outlining the bare minimum for every patient with lung cancer (e.g., testing based on clinical guidelines, acceptable turnaround time, and maximum out-of-pocket expense, etc.).
- Generate sample legislation language to assure biomarker testing.

to describe biomarker testing in the literature. For patients and family members to gain functional health literacy related to their diagnosis of lung cancer, they must gain familiarity with medical terminology, a task made more difficult by inconsistent language.[20–22] The ACS NLCRT has adopted the term *comprehensive biomarker testing* for the process that, at a minimum, assesses for all possible guideline-recommended and actionable biomarkers for a patient's lung cancer subtype and will work to engage the appropriate professional societies to consistently use this term.

To achieve universal comprehensive biomarker testing that will enable appropriate personalized therapy for patients with lung cancer, their physicians must have sufficient knowledge to inform decision making. Physicians and patients may be faced with a variety of complex decisions regarding testing, including biomarker testing indicated for a particular subtype of lung cancer, the optimal approach to tissue acquisition, which biomarkers to test for, whether to re-biopsy if the first attempt was unable to obtain sufficient tumor tissue for testing, and whether to delay treatment while awaiting test results.[23] The rapid evolution of evidence demonstrating the benefits of biomarker testing and subsequent treatment with appropriate therapies creates a knowledge gap that constitutes a barrier to widespread adoption of precision medicine for patients with lung cancer. Furthermore, surveys of physicians demonstrate they have low confidence in interpreting genomic test results.[24–27] This burden of knowledge on patients and physicians must be reduced.

Clinical guidelines recommend broad panel testing for all patients with newly diagnosed NSCLC.[10,11] Despite this recommendation, retrospective studies reveal disparities in testing practices, demonstrating higher rates of biomarker testing for *EGFR* mutations in women, Asians, and persons who have never smoked.[4,6,28,29] This particular testing strategy is an antiquated legacy of the early association between these characteristics and increased chances of response to anti-EGFR tyrosine kinase inhibitor therapy before the discovery of their association with activating mutations of *EGFR* were discovered in 2004.[30–32] The explanation for other patterns of

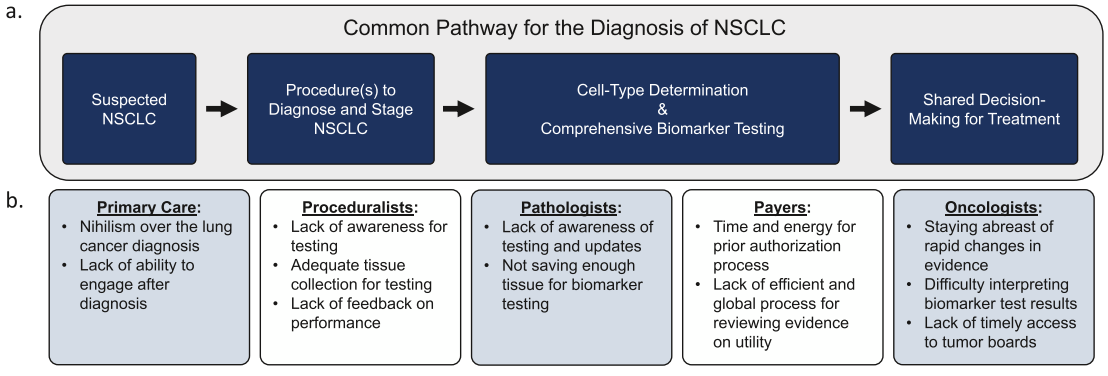

FIGURE 1 (A) The common steps or diagnostic pathway patients undergo from suspicion of lung cancer to treatment for those with advanced non–small cell lung cancer and (B) barriers to comprehensive biomarker testing experienced by individual groups that were identified during the confessional session of the Summit on Optimizing Lung Cancer Biomarkers in Practice.

disparities in testing, including lower rates of testing of racial minorities, the underinsured, persons with more comorbidities, and geographic differences, are less clear and likely multifaceted.[8,33–35] These disparities suggest that some physicians lack sufficient knowledge not only of the indications and clinical guidelines required to achieve universal comprehensive biomarker testing but also of the existence of financial and socioeconomic barriers.

The use of demographic factors to direct *EGFR* testing for patients with nonsquamous NSCLC is specifically discouraged by the 2013 CAP/IASLC/AMP guidelines.[36] The updated 2018 CAP/IASLC/AMP guidelines, also endorsed by the American Society of Clinical Oncology (ASCO), affirm this recommendation, labeling *EGFR*, *ALK*, and *ROS1* as *must-test* biomarkers for all patients who have newly diagnosed NSCLC with an adenocarcinoma component and tumors with a diagnosis of NSCLC not otherwise specified at that time.[10,37] The 2018 CAP/IASLC/AMP guidelines were finalized in the Spring of 2017. The authors designated biomarkers as *must-test* based on then-existing evidence from clinical trials and FDA drug approvals. Multiple biomarker-driven therapies have since emerged from clinical trials completed since the issue of those guidelines, including additional FDA approvals. The list of *must-test* biomarkers has to be continuously updated. *HER2/ERBB2*, *MET* (particularly the exon 14 splicing mutation), *BRAF*, and *KRAS* mutations and *NTRK* and *RET rearrangements* are now additional *must-test* biomarkers that must be included in comprehensive biomarker tests and are typically included in next-generation sequencing (NGS) panels. The increasing availability of panel testing and NGS should allow for easier assessment of all actionable biomarkers.

Although the influence of physician knowledge on the rate of biomarker testing has been documented, less is known about how patient knowledge and preferences affect biomarker testing. In one survey of 293 oncologists caring for patients with colorectal cancer or NSCLC, 16% of respondents reported that patient requests highly influenced their decisions to order testing.[38] Patients are likely poorly informed about biomarker testing, and one study of participants enrolled in a biomarker-driven clinical trial demonstrated that many patients have misconceptions about testing.[39] In addition, many lung cancer advocacy groups, including the ACS, value and support patient education as a tool to help expand testing.[40] Dissemination and educational efforts directed at patients may increase testing by supporting self-advocacy.

Recommendation 1: Disseminate clear and consistent educational materials for biomarker testing to physicians and patients

A working group within the Triage for Appropriate Therapy Task Group within the ACS NLCRT has been charged with creating educational materials for patients and physicians. The ACS NLCRT supports patient and family education on comprehensive biomarker testing, allowing them to serve as advocates for their own care. These materials must be well organized, concise, regularly updated, individualized to the target audience, and contain key information, such as indications and benefits. They must use simple, common, and consistent terminology, which is critical to improve communication, provide clarity, and avoid confusion. The Triage for Appropriate Treatment Task Group of the ACS NLCRT supports including patient stories in these educational materials as critical to inspire both patients and physicians struggling with the nihilism related to the efficacy of treatment of lung cancer. In its partnership with other organizations and professional societies, the ACS NLCRT will promote the use of consistent terminology and advocate for uniformity in educational materials, the presentation of testing results, and clinical guidelines.

Key challenge 2: Procurement of adequate tissue for comprehensive biomarker testing

Ensuring timely collection of adequate tumor tissue to perform comprehensive biomarker testing should be a priority for any physician performing diagnostic procedures for lung cancer. Tissue adequacy for testing is a critical issue for implementing personalized medicine for lung cancer. A study of 2000 consecutive attempts between 2012 and 2013 at multiplex genomic panel testing for all cancers reported a 23% failure rate because of insufficient tissue at a single academic center in the United States.[41] Failure to collect adequate tissue is a consistent problem in studies assessing rates of testing in NSCLC as well. Approximately one fifth of attempts at biomarker testing for NSCLC failed because of inadequate tissue in two cohorts from academic centers in the United States.[42,43] In a 2-year series of *EGFR* testing in a single health care network, 7.2% of samples lacked sufficient tissue for testing, and 124 of 2293 (5.4%) samples analyzed had inconclusive results.[44] A study of biomarker testing in a European hospital system from 2008 to 2014 reported that 10.5% of patients tested had insufficient tissue. Although rates improved over the study period, there was significant variation in the rate of biomarker testing between the four participating hospitals.[45] Since the advent of biomarker-driven therapies for NSCLC, adequate tissue collection for testing has consistently been a significant quality-assurance problem.

Tissue availability depends on several factors, including the type of samples taken, the quantity of tissue expended to establish a diagnosis, and the chosen assay's requirements. The general approach to choosing an invasive diagnostic testing modality is to identify a lesion that would result in the highest yield of tissue for diagnosis and biomarker testing with the greatest margin for safety, acknowledging local constraints with respect to resources and expertise. A tumor core biopsy is commonly the preferred diagnostic sample for histology and immunohistochemical and biomarker assessment. However, with careful tissue management, minimally invasive biopsy approaches using fine-needle aspirates can enable successful biomarker testing. In a series of >1000 patients at a single center from 2004 to 2017, test failure rates ranged from <5% to 13% with two thirds of all samples consisting of cytology and small

biopsies.[4] A meta-analysis, including 33 studies and 2698 patients, demonstrated successful *EGFR* testing for 94.5% (95% CI, 93.2%–96.4%) of fine-needle aspirates acquired by bronchoscopy with endobronchial ultrasound and transbronchial needle biopsy.[46] However, success rates likely vary between institutions. In a single-center study of NGS, success rates were 11 of 33 (33%) for fine-needle aspirates, 47 of 61 (66%) for endoscopic biopsies, and 99 of 104 (95%) for excisional biopsies.[42] Different testing strategies, assays, and platforms require different amounts of tumor tissue, further complicating the definition of what constitutes an adequate sample. Although changes in the number of biomarkers, testing strategies, and assays over the last decade make for difficult comparisons between studies, inadequate tissue remains an issue for comprehensive biomarker testing.

Inadequate tissue procurement is partly driven by a lack of awareness of the need for comprehensive biomarker testing and partly by service constraints. For instance, there is variation among pulmonologists in their knowledge of guidelines for performing lymph node sampling during bronchoscopy and in their access to technologies, such as rapid onsite cytology evaluation by pathologists to help ensure adequacy of tumor tissue.[47] Experienced pathologists can assist with determining the adequacy of specimens by assessing histology features, such as viable malignant cell content and the extent of necrosis at the time of biopsy. Pulmonologists with interventional subspecialty training were more likely to be aware of guidelines, diagnose more lung cancers, and make more passes during fine-needle aspiration than their general pulmonologist counterparts. This variation likely also applies to other specialties, such as radiologists and surgeons, who may have inconsistent education, training, and exposure to the diagnosis and treatment of lung cancer in the setting of new treatment paradigms.

Recommendation 2: Provide education to proceduralists performing tissue sampling for potential lung cancer and guide the development of institutional policies promoting adequate tissue collection

All proceduralists performing diagnostic tissue sampling for lung cancer need to be informed about the importance of obtaining adequate amounts of tissue for comprehensive biomarker testing within their institutions and community. This local collaboration is paramount because the amount of tissue needed may vary based on the methods used to perform testing. A subgroup of the ACS NLCRT Triage for Appropriate Treatment Task Group is working to propose performance benchmarks for successful completion of biomarker testing. An area of future research is whether patients are best served by referral to physicians specialized in diagnosing lung cancer or whether education and training should be provided to less specialized physicians currently lacking the necessary knowledge and expertise.

Key challenge 3: Choice of assay, testing strategy, and turnaround time

Assay choice and testing strategy

Assay choice and biomarker testing strategy in NSCLC are driven by the need to balance multiple factors, including access to testing methods, the amount of tissue needed for testing, turnaround time, cost, comprehensiveness of the test, and third-party coverage. In addition to the variety of assays, platforms, and testing strategies, physicians and their institutions will have variable priorities and resources that lead to practice differences, some of which may be unknowingly detrimental to patient care.[48,49] A recent survey of >400 pulmonologists in the United States illustrated variation in the subspecialty of the provider who orders testing at different institutions.[47] Respondents identified oncologists as most frequently responsible (37%), followed by pathologists, pulmonologists, and tumor boards (31%, 23%, and 7%, respectively). The workflow for testing has obvious implications for costs, logistics, turnaround time, and insurance coverage, so institutions vary in their practice. In the same survey of pulmonologists, 20% reported in-house testing, 44% reported outside testing, and 31% reported a combination of the two. Results from a worldwide survey of >2500 participants from multiple specialties involved in the diagnose or treatment of lung cancer found comparable results, with 30% in-house testing, 43% outsourced testing, and 28% a combination of the two.[8] Determining the ideal assay and testing strategy requires that physicians and institutions factor in many variables, which may have competing interests.

Joint CAP/IASLC/AMP and NCCN guidelines support the use of broad panels or NGS, but there is a paucity of supporting evidence for the optimal testing strategy, the process or order in which available assays are performed.[10,11] Available assays for biomarker testing include single gene mutation tests, smaller panels (<50 genes), and larger panels (50 to ≥1000 genes). Further complicating matters, different techniques and platforms can be used to detect oncogenic drivers in tumor tissue. For example, the most recent ASCO guidelines state that immunohistochemistry can be used as a *screening* test for *ROS1* rearrangements but that they should be confirmed by a cytogenetic or other molecular method, such as fluorescence in situ hybridization, reverse transcription polymerase chain reaction, or NGS.[10,37] Some advocate for testing for the most common mutations in sequential order because these mutations are mutually exclusive.[50] Mutations would be tested in order only when the preceding priority mutation was not found. Although this approach may seem to potentially avoid the expense of broad panel testing, it is likely to limit the detection of relatively infrequent sensitizing mutations, to be associated with unacceptably long turnaround time, and might ultimately prove to be more expensive.

As the list of available biomarkers and their associated therapeutics grows, it is increasingly evident that the need for rapid comprehensive testing of an ever-expanding panel of biomarkers is required. One multicenter study routinely assessed driver mutations in >1000 lung cancers using several non-NGS assays and

demonstrated driver mutations in 64% of cases, leading to targeted therapies in 28% of patients.[51] In >70% of cases, they were successful in assessing all 10 candidate driver mutations. Coupling the massive parallel sequencing of NGS with bioinformatics allows an assessment of mutations and genetic aberrations on an in-depth, broad scale and may require less tissue than other methods. NGS can be performed reliably on small biopsies, including fine-needle aspirates, and requires as little as 50 ng of tumor DNA.[52] NGS testing strategies include whole genome sequencing, whole exome sequencing, whole transcriptome sequencing, and targeted *hot-spot* testing, among others. Each strategy has different implications for cost, tumor tissue requirement, and amount of data produced.[53,54] A single-center study in which NGS was used to reassess 31 patients who had already undergone non-NGS biomarker testing demonstrated that 26% had actionable mutations only discovered by NGS.[55] New methods for panel testing, such as NGS, likely provide improved sensitivity with broader and more timely results compared with sequential and smaller testing strategies, especially as the recommended number of biomarkers to test continues to grow.

Some argue that the cost of NGS is not justified by the relatively small number of actionable mutations in the absence of proof of population benefit.[56] Comparing NGS with other testing modalities can be complex given the other variables involved, such as turnaround time; comprehensiveness of testing; upstream costs, such as equipment; downstream costs, such as data storage; and the financial impact of treatment decisions, including the cost of targeted therapeutics.[57] With these barriers in mind, there are models demonstrating that NGS is cost effective for both government and commercial payers.[58] The ACS NLCRT Triage for Appropriate Treatment Task Group supports the use of NGS, when available, because it provides timely and comprehensive biomarker testing for patients and is also well suited to adapt to the rapid, expansive growth of biomarkers and targeted therapeutics.

Turnaround time

Turnaround time of biomarker testing results is a complex problem that depends on assay choice and testing strategy. There is a plethora of logistical and tissue handling factors that will vary in different practices and from institution to institution. The ASCO and CAP/IASCL/AMP guidelines suggest that any testing method and strategy should have a turnaround time of 2 weeks (10 working days) or less, from sample receipt by the laboratory to reporting of all results.[10,37] However, this timeframe does not account for delays in ordering, transportation of specimens, or acting on results when they are available. Although some centers report turnaround times well within the recommended 10-day window, these centers may have resources that are not widely available, and their methods may not be generalizable across other health care systems.

Timely turnaround of results has important implications for patient care. One single-center study from 2010 to 2013 showed that molecular results were only available by the first oncologist appointment in 21% of cases.[29] There is evidence from retrospective series to suggest that long turnaround times pressure multidisciplinary tumor boards and oncologists to pursue potentially inferior nontargeted therapies rather than waiting for test results.[23,29,59] In a large European cohort from 2012 to 2013 consisting of >17,000 patients, mostly with advanced disease, biomarker test results informed first-line therapy in 51% of >8000 patients for whom these data were known. For the almost 4000 patients for whom test results did not inform first-line therapies, length of turnaround time was cited as the reason for almost one quarter of the cases.[59] Initiating treatment before biomarker results limits patients to nontargeted chemotherapy in nonsquamous NSCLC because these therapies may be detrimental in the absence of a positive biomarker test. This was illustrated in a subgroup analysis of the iPASS trial (ClinicalTrials.gov identifier NCT00322452), in which patients without *EGFR* mutations who received gefitinib had shorter progression-free survival than those who received carboplatin–paclitaxel.[60] Furthermore, tyrosine kinase inhibitor therapy after prior systemic therapy with immune checkpoint inhibitors (with or without chemotherapy) is associated with an increased risk for severe pneumonitis, limiting safe use.[61] In addition to the implications for physicians' decisions regarding initiation of therapy, the wait period for molecular testing causes psychological stress for patients.[62] Successful implementation of comprehensive biomarker testing and deployment of therapies based on the results requires a clinically acceptable turnaround time of results.

Liquid biopsy

Analysis of circulating tumor DNA from peripheral blood specimens (*liquid biopsy*) is rapidly establishing a role in detecting actionable mutations in NSCLC. Emerging applications for this approach include screening, monitoring treatment response (including the presence of minimal residual disease after curative-intent treatment or early detection of disease progression), and identifying mechanisms of resistance. Relative to tissue biopsy, these assays offer benefits, including ease and convenience of a blood draw, quick turnaround time, and a high specificity, which indicates a high positive predictive value when actionable mutations are identified.[63] Current common practices using liquid biopsy capitalize on these advantages. For instance, when there is clinical urgency to initiate therapy or when tissue is inadequate for biomarker testing, liquid biopsy may identify actionable mutations that can direct treatment decisions. It is worth noting that there is no current role for liquid biopsy to replace initial tissue biopsy to confirm a pathologic diagnosis and attempt to complete comprehensive biomarker testing. Limitations include inability to assess non-DNA biomarkers, including PD-L1 status, cost, and lower sensitivity compared with tissue-based tests.[64] Given the potential for false-negative results, tissue sampling should be considered when initial liquid biopsy results are negative.[65] The role of liquid biopsies is likely to expand rapidly in coming years given the intensity of ongoing clinical trials activity.

Recommendation 3: Promote the use of guideline-driven biomarker panel testing through testing algorithms and implementation of reflex testing

A subgroup of the ACS NLCRT Triage for Appropriate Treatment Task Group is charged with creating a *Clinical Guide to Comprehensive Testing Biomarker Testing* to aid physicians' understanding of fundamentals and critical aspects of successful testing. Creation of accepted testing algorithms and flow diagrams for optimal biomarker testing will likely aid physicians in their ordering practices. Equipping physicians with easy-to-follow decision tools for choosing the optimal biomarker testing strategy may encourage testing.

A reflex testing strategy, in which biomarkers are automatically ordered and tested for newly diagnosed patients, is a strategy that may facilitate timely testing. Algorithms or collaborative policies for newly diagnosed patients can eliminate the ordering step and reduce the time to test initiation. In one single center's experience with 306 patients during implementation of a reflex testing strategy, testing for *EGFR* increased from 70% to 95% and testing for *ALK* increased from 44% to 83% in patients with advanced, nonsquamous NSCLC ($p < .001$).[66] In addition, the time to optimal treatment was shorted from a median of 36 days to 24 days ($p = .036$). In another, more recent report, reflex testing was implemented alongside changes in testing methodologies, resulting in improved turnaround time by 36 days.[67] As the complexity and continual evolution of the biomarker landscape in NSCLC continues to pose a barrier to implementation, reflex testing has demonstrated success for improving key metrics, and its use is supported by the Triage for Appropriate Treatment Task Group.

Key challenge 4: Physicians have difficulty accurately interpreting biomarker testing results

To capitalize on the benefits of comprehensive biomarker testing, physicians must be able to interpret test results and translate them into evidence-based clinical decisions regarding targeted therapy or immunotherapy. Evidence suggests physicians have problems interpreting biomarker test results. A recent global multidisciplinary survey of lung cancer clinicians found that over one third of respondents who order biomarker tests or treat patients with lung cancer reported trouble interpreting test results, many noting gaps in their technical and scientific knowledge.[8] One survey of >1000 oncologists demonstrated that confidence in interpreting tests varied by the type of assay used. Respondents with higher patient volumes and any reported genomic training reported greater confidence interpreting results.[27]

In the setting of broad panel testing, higher volumes of information must be processed by treating physicians. Test reports may not include guidance on how the results may support specific treatments and may not be trusted if they are included.[68] Reports may show more than just actionable biomarkers. For instance, some panels may report *variants of uncertain clinical significance*, which may be under investigation as prognostic indicators, potential future drug targets, or germline polymorphisms. Another example of the complexity facing physicians is illustrated by the multiple companion tests for PD-L1/PD-1 immunotherapy, each of which has different cutoff values for stratifying whether patients are eligible for single-agent treatment.[69] Some institutions and professional societies have developed genetic tumor boards to aid physicians in interpreting test results.[25,70] Although evidence suggests that physicians have problems interpreting and acting on test results, the exact issues they experience and how to overcome them are thus far poorly defined, not well understood, and warrant further investigation.

Recommendation 4: Encourage standardized biomarker test reports and develop algorithms that aid in directing treatment

It can be a challenge to translate complex test results into clinical decisions. Lack of confidence in effectively using the results of biomarker testing may inhibit some providers from testing or optimally using the information to provide the best possible treatment. Standardizing biomarker test results along with associated treatment algorithms may improve testing and decision making. ACS NLCRT initiatives, including promotion of common terminology, education and dissemination efforts, and development of evidence-based clinical decision tools, aim to help physicians interpretate results.

Key challenge 5: Reimbursement, cost, and coverage

Problems with assuring third-party coverage and reimbursement generate potentially significant barriers or delays to comprehensive biomarker testing. Despite health economic evidence that supports the use of comprehensive biomarker testing, attendees of the Biomarker Summit cited coverage and reimbursement as a significant problem. Several changes made by the Centers for Medicare & Medicaid Services (CMS) in recent years have reduced reimbursement barriers. As of January 2018, revisions to the Medicare Hospital Outpatient Prospective Payment System and the Laboratory date of service regulation (42 Code of Federal Regulations §414.510), or *the 14-day rule*, allow for laboratories to bill Medicare directly for biomarker testing.[71] Essentially, before this revision, if biomarker testing was ordered within 14 days of an outpatient procedure, the hospital would not be specifically reimbursed by the CMS for this expense. This regulation previously led to concerns that testing was being delayed until after the 14-day window from the procedure, delaying results and treatment. Notably, the 14-day rule still applies to newly diagnosed NSCLC in the inpatient setting. As of March 2018, the CMS also took a step forward by covering FDA-approved NGS tests for patients with recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer.[72] Despite improvements made by the CMS, coverage by private insurers remain variable.

The frequent requirement of prior authorization for biomarker testing delays testing, thus increasing the turnaround time and hindering treatment decisions. In addition, the prior authorization process can put a burden on physicians and their practices, which could discourage testing. During the Biomarker Summit, payer representatives stressed that, for payers to feel confident that coverage of biomarker testing is indicated, beneficial, and necessary, they must be provided with evidence that testing leads to clinically meaningful benefit. The NCCN guidelines support the use of broad molecular profiling but do not provide guidance on what constitutes *broad* testing. This issue is consistent with the need for common and consistent terminology discussed above in Recommendation 1. There also are numerous Current Procedural Terminology codes for single-gene assays but only two for multigene panels, one for panels of <50 genes and another for >50 genes. This lack of definition by Current Procedural Terminology code further complicates payer decisions on whether to reimburse.

Recommendation 5: Remove the disconnect between payer policies and evidence-based guidelines for comprehensive biomarker testing to increase coverage and avoid delays

Discussions at the Biomarker Summit revealed that payers face many of the same problems encountered by patients and physicians in understanding indications for biomarker testing, interpretation of their results, and evidence of beneficial impact on patient care. Payers must be provided tools and evidence similar to those provided to physicians and patients that help simplify both terminology and optimal biomarker testing strategies. A subgroup of the Triage for Appropriate Treatment Task Group will develop a standardized evidence guide to aid third-party coverage decisions and preauthorization algorithms for biomarker testing. Clear, evidence-based decision tools should facilitate payer decision making and increase coverage and reimbursement for these services. In addition, the ACS NLCRT will generate sample legislation with language that assures biomarker testing for those patients with NSCLC who may benefit from testing.

Emerging challenges

Many of the challenges to achieve comprehensive biomarker testing for all patients with advanced NSCLC arise from rapid evolution in the field. Liquid biopsy for biomarker testing offers increased access and opportunity for patients, and ongoing research will establish its role and best practices for use. Recent trials also have provided evidence for treatment with targeted therapy and immunotherapy in the adjuvant and neoadjuvant settings for earlier stages of NSCLC, in some cases leading to FDA approvals.[1,73,74] As the indications for biomarker-directed treatment expand across the stage spectrum, the convenience and justification for reflex comprehensive biomarker testing will become even greater.

CONCLUSION

The ACS NLCRT is committed to the goal of universal comprehensive biomarker testing for patients with NSCLC. To further this mission, the ACS NLCRT held the Biomarker Summit in September 2020 to create common understanding of the most important barriers and to foster collaboration on strategies to facilitate testing. The ACS NLCRT's Strategic Plan to Advance Biomarker Testing for all eligible patients with NSCLC prioritizes initiatives and projects developed at the Biomarker Summit to surmount the key challenges to achieving universal comprehensive biomarker testing.

AUTHOR CONTRIBUTIONS

Adam H. Fox and **Gerard A. Silvestri** lead the composition, literature review, and submission of the article. All coauthors made significant contributions to the composition and revisions of the article.

ACKNOWLEDGMENTS

This work was supported by K12 CA157688 (Adam H. Fox), the Alice and Stephen D. Cutler Fund (Bruce E. Johnson), and the Satherlie Family Research Fund (Bruce E. Johnson). The ACS receives funding support for the ACS NLCRT from AbbVie, Amgen, AstraZeneca, Daiichi-Sankyo, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Foundation Medicine, Genentech, Guardant Health, Johnson & Johnson, Merck, Novartis, Novocure, Regeneron, Roche, Sanofi-Genzyme, and Takeda. Role of sponsors: The sponsors had no role in the design of the study, the collection, and analysis of the data, or the preparation of the manuscript.

CONFLICTS OF INTEREST

Adam H. Fox owns stock in Merck. Raymond U. Osarogiagbon owns patents for a lymph node specimen collection kit; owns stocks in Eli Lilly, Gilead Sciences, and Pfizer; reports personal fees as a paid research consultant for the American Cancer Society, the Association of Community Cancer Centers, AstraZeneca, Biodesix, Eli Lilly, Triptych Healthcare Partners, Genentech/Roche, and the National Cancer Institute outside the submitted work; is founder of Oncobox Device, Inc.; and reports funding from the National Institutes of Health (UG1CA189873, R01CA172253, and UM1CA233080) outside the submitted work. James R. Jett reports honoraria from UpToDate for editorial activities outside the submitted work and is co-chief medical officer for and owns stock in Biodesix, Inc. Bruce E. Johnson reports postmarketing royalties from the Dana-Farber Cancer Institute for *EGFR* mutation testing, is a paid consultant for the American Cancer Society, and is a consultant for Daiichi Sankyo and Astra Zeneca all outside the submitted work. M. Patricia Rivera reports funding from the National Institutes of Health/National Cancer Institute Scientific and Medical Advisory Board, Biodesix, and bioAffinity outside the submitted work. Robert A. Smith reports that the American Cancer Society receives unrestricted educational funding from Amgen, AstraZeneca, Bristol-Myers Squibb, Foundation Medicine, Genentech, Guardant Health, Lilly, and Merck to support ACS NLCRT. Ignacio I. Wistuba reports grants and personal fees from Genentech/Roche,

Bayer, Bristol-Myers Squibb, AstraZeneca, Pfizer, HTG Molecular Merck, GlaxoSmithKline, Guardant Health, Novartis, Sanofi, and Amgen; grants from Adaptive, Adaptimmune, EMD Serono, Takeda, Karus, Johnson & Johnson, 4D, Iovance, and Akoya; and personal fees from Asuragen, Flame, Daiichi Sankyo, Oncocyte, MSD, and Platform Health outside the submitted work. Gerard A. Silvestri reports research support from Exact Sciences; personal fees and research support from Amgen, Biodesix, Nucleix, and the National Cancer Institute's Surveillance, Epidemiology and End Results Program; and is the recipient of a Paul Calabresi K12 Career Development Award (K12-CA157688), all outside the submitted work. Farhood Farjah made no disclosures.

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REFERENCES

1. Wu YL, Tsuboi M, He J, et al. Osimertinib in resected *EGFR*-mutated non–small-cell lung cancer. *N Engl J Med*. 2020;383(18):1711-1723. doi:10.1056/NEJMoa2027071
2. Howlader N, Forjaz G, Mooradian MJ, et al. The effect of advances in lung-cancer treatment on population mortality. *N Engl J Med*. 2020;383(7):640-649. doi:10.1056/NEJMoa1916623
3. Brahmer JR, Rodriguez-Abreu D, Robinson AG, et al. Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial. *Lancet Oncol*. 2017;18(12):1600-1609. doi:10.1016/s1470-2045(17)30690-3
4. VanderLaan PA, Rangachari D, Majid A, et al. Tumor biomarker testing in non-small-cell lung cancer: a decade of change. *Lung Cancer*. 2018;116:90-95. doi:10.1016/j.lungcan.2018.01.002
5. Waterhouse DM, Tseng WY, Espirito JL, Robert NJ. Understanding contemporary molecular biomarker testing rates and trends for metastatic NSCLC among community oncologists. *Clin Lung Cancer*. 2021;22(6):e901-e910. doi:10.1016/j.cllc.2021.05.006
6. John A, Shah RA, Wong WB, Schneider CE, Alexander M. Value of precision medicine in advanced non-small cell lung cancer: real-world outcomes associated with the use of companion diagnostics. *Oncologist*. 2020;25(11):e1743-e1752. doi:10.1634/theoncologist.2019-0864
7. Mason C, Ellis PG, Lokay K, et al. Patterns of biomarker testing rates and appropriate use of targeted therapy in the first-line, metastatic non-small cell lung cancer treatment setting. *J Clin Pathw*. 2018;4(1):49-54. doi:10.25270/jcp.2018.02.00001
8. Smeltzer MP, Wynes MW, Lantuejoul S, et al. The International Association for the Study of Lung Cancer global survey on molecular testing in lung cancer. *J Thorac Oncol*. 2020;15(9):1434-1448. doi:10.1016/j.jtho.2020.05.002
9. Gutierrez ME, Choi K, Lanman RB, et al. Genomic profiling of advanced non-small cell lung cancer in community settings: gaps and opportunities. *Clin Lung Cancer*. 2017;18(6):651-659. doi:10.1016/j.cllc.2017.04.004
10. Lindeman NI, Cagle PT, Aisner DL, et al. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. *Arch Pathol Lab Med*. 2018;142(3):321-346. doi:10.5858/arpa.2017-0388-CP
11. National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer*. Version 3. NCCN; 2021.
12. Han JY, Kim SH, Lee YS, et al. Comparison of targeted next-generation sequencing with conventional sequencing for predicting the responsiveness to epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) therapy in never-smokers with lung adenocarcinoma. *Lung Cancer*. 2014;85(2):161-167. doi:10.1016/j.lungcan.2014.04.009
13. Schatz S, Falk M, Jori B, et al. Integration of tumor mutation burden and PD-L1 testing in routine laboratory diagnostics in non-small cell lung cancer. *Cancers (Basel)*. 2020;12(6):1685. doi:10.3390/cancers12061685
14. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, *EGFR*-mutated advanced NSCLC. *N Engl J Med*. 2020;382(1):41-50. doi:10.1056/NEJMoa1913662
15. Mok T, Camidge DR, Gadgeel SM, et al. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced *ALK*-positive non-small-cell lung cancer in the ALEX study. *Ann Oncol*. 2020;31(8):1056-1064. doi:10.1016/j.annonc.2020.04.478
16. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol*. 2008;26(21):3543-3551. doi:10.1200/jco.2007.15.0375
17. Berardi R, Morgese F, Rinaldi S, et al. Benefits and limitations of a multidisciplinary approach in cancer patient management. *Cancer Manag Res*. 2020;12:9363-9374. doi:10.2147/cmar.S220976
18. Denton E, Conron M. Improving outcomes in lung cancer: the value of the multidisciplinary health care team. *J Multidiscip Healthc*. 2016;9:137-144. doi:10.2147/jmdh.S76762
19. Ray MA, Faris NR, Fehnel C, et al. Survival impact of an enhanced multidisciplinary thoracic oncology conference in a regional community health care system. *JTO Clin Res Rep*. 2021;2(8):100203. doi:10.1016/j.jtocrr.2021.100203
20. Fage-Butler AM, Nisbeth Jensen M. Medical terminology in online patient-patient communication: evidence of high health literacy? *Health Expect*. 2016;19(3):643-653. doi:10.1111/hex.12395
21. Davis TC, Williams MV, Marin E, Parker RM, Glass J. Health literacy and cancer communication. *CA Cancer J Clin*. 2002;52(3):134-149. doi:10.3322/canjclin.52.3.134
22. Pieterse AH, Jager NA, Smets EM, Henselmans I. Lay understanding of common medical terminology in oncology. *Psychooncology*. 2013;22(5):1186-1191. doi:10.1002/pon.3096
23. Mileham KF, Schenkel C, Bruinooge SS, et al. Defining comprehensive biomarker-related testing and treatment practices for advanced non-small-cell lung cancer: results of a survey of U.S. oncologists. *Cancer Med*. 2022;11(2):530-538. doi:10.1002/cam4.4459
24. Sholl LM, Do K, Shivdasani P, et al. Institutional implementation of clinical tumor profiling on an unselected cancer population. *JCI Insight*. 2016;1(19):e87062. doi:10.1172/jci.insight.87062
25. Bryce AH, Egan JB, Borad MJ, et al. Experience with precision genomics and tumor board, indicates frequent target identification, but barriers to delivery. *Oncotarget*. 2017;8(16):27145-27154. doi:10.18632/oncotarget.16057
26. Gray SW, Hicks-Courant K, Cronin A, Rollins BJ, Weeks JC. Physicians' attitudes about multiplex tumor genomic testing. *J Clin Oncol*. 2014;32(13):1317-1323. doi:10.1200/jco.2013.52.4298
27. de Moor JS, Gray SW, Mitchell SA, Klabunde CN, Freedman AN. Oncologist confidence in genomic testing and implications for using multimarker tumor panel tests in practice. *JCO Precis Oncol*. 2020;4(4):620-631. doi:10.1200/po.19.00338

28. Sacher AG, Dahlberg SE, Heng J, Mach S, Janne PA, Oxnard GR. Association between younger age and targetable genomic alterations and prognosis in non-small-cell lung cancer. *JAMA Oncol*. 2016;2(3):313-320. doi:10.1001/jamaoncol.2015.4482
29. Lim C, Tsao MS, Le LW, et al. Biomarker testing and time to treatment decision in patients with advanced non–small-cell lung cancer. *Ann Oncol*. 2015;26(7):1415-1421. doi:10.1093/annonc/mdv208
30. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004;350(21):2129-2139. doi:10.1056/NEJMoa040938
31. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004;304(5676):1497-1500. doi:10.1126/science.1099314
32. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci U S A*. 2004;101(36):13306-13311. doi:10.1073/pnas.0405220101
33. Palazzo LL, Sheehan DF, Tramontano AC, Kong CY. Disparities and trends in genetic testing and erlotinib treatment among metastatic non-small cell lung cancer patients. *Cancer Epidemiol Biomarkers Prev*. 2019;28(5):926-934. doi:10.1158/1055-9965.Epi-18-0917
34. Lynch JA, Berse B, Rabb M, et al. Underutilization and disparities in access to EGFR testing among Medicare patients with lung cancer from 2010–2013. *BMC Cancer*. 2018;18(1):306. doi:10.1186/s12885-018-4190-3
35. Kehl KL, Lathan CS, Johnson BE, Schrag D. Race, poverty, and initial implementation of precision medicine for lung cancer. *J Natl Cancer Inst*. 2019;111(4):431-434. doi:10.1093/jnci/djy202
36. Lindeman NI, Cagle PT, Beasley MB, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Thorac Oncol*. 2013;8(7):823-859. doi:10.1097/JTO.0b013e318290868f
37. Kalemkerian GP, Narula N, Kennedy EB, et al. Molecular testing guideline for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors: American Society of Clinical Oncology endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology clinical practice guideline update. *J Clin Oncol*. 2018;36(9):911-919. doi:10.1200/jco.2017.76.7293
38. Gray SW, Kim B, Sholl L, et al. Medical oncologists' experiences in using genomic testing for lung and colorectal cancer care. *J Oncol Pract*. 2017;13(3):e185-e196. doi:10.1200/jop.2016.016659
39. Roth JA, Trivedi MS, Gray SW, et al. Patient knowledge and expectations about return of genomic results in a biomarker-driven master protocol trial (SWOG S1400GEN). *JCO Oncol Pract*. 2021;17(11):e1821-e1829. doi:10.1200/OP.20.00770
40. Aldigé C, Roy UB, Boerckel W, et al. The Role of Lung Cancer Advocacy Organizations in Biomarker Testing. *CancerCare*; 2018. Accessed Febuary 1, 2022. https://media.cancercare.org/publications/original/386-2018_lungroundtable.pdf
41. Meric-Bernstam F, Brusco L, Shaw K, et al. Feasibility of large-scale genomic testing to facilitate enrollment onto genomically matched clinical trials. *J Clin Oncol*. 2015;33(25):2753-2762. doi:10.1200/jco.2014.60.4165
42. Hagemann IS, Devarakonda S, Lockwood CM, et al. Clinical next-generation sequencing in patients with non-small cell lung cancer. *Cancer*. 2015;121(4):631-639. doi:10.1002/cncr.29089
43. DiStasio M, Chen Y, Rangachari D, Costa DB, Heher YK, VanderLaan PA. Molecular testing turnaround time for non-small cell lung cancer in routine clinical practice confirms feasibility of CAP/IASLC/AMP guideline recommendations: a single-center analysis. *Clin Lung Cancer*. 2017;18(5):e349-e356. doi:10.1016/j.cllc.2017.03.001
44. Shiau CJ, Babwah JP, da Cunha Santos G, et al. Sample features associated with success rates in population-based EGFR mutation testing. *J Thorac Oncol*. 2014;9(7):947-956. doi:10.1097/jto.0000000000000196
45. Sluga R, van den Borne BEEM, Roepman P, Peters BJM, Kastelijn EA, Schramel FMNH. Utilization of molecular testing and survival outcomes of treatment with first- or second-line tyrosine kinase inhibitors in advanced non-small cell lung cancer in a Dutch population. *Anticancer Res*. 2018;38(1):393-400. doi:10.21873/anticanres.12235
46. Labarca G, Folch E, Jantz M, Mehta HJ, Majid A, Fernandez-Bussy S. Adequacy of samples obtained by endobronchial ultrasound with transbronchial needle aspiration for molecular analysis in patients with non-small cell lung cancer. Systematic review and meta-analysis. *Ann Am Thorac Soc*. 2018;15(10):1205-1216. doi:10.1513/AnnalsATS.201801-045OC
47. 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. *Chest*. 2021;160(6):2293-2303. doi:10.1016/j.chest.2021.06.027
48. Lipitz-Snyderman A, Sima CS, Atoria CL, et al. Physician-driven variation in nonrecommended services among older adults diagnosed with cancer. *JAMA Intern Med*. 2016;176(10):1541-1548. doi:10.1001/jamainternmed.2016.4426
49. Richards JM, Burgon TB, Tamondong-Lachica D, et al. Reducing unwarranted oncology care variation across a clinically integrated network: a collaborative physician engagement strategy. *J Oncol Pract*. 2019;15(12):e1076-e1084. doi:10.1200/jop.18.00754
50. Layfield LJ, Hammer RD, White SK, Furtado LV, Schmidt RL. Molecular testing strategies for pulmonary adenocarcinoma: an optimal approach with cost analysis. *Arch Pathol Lab Med*. 2019;143(5):628-633. doi:10.5858/arpa.2018-0218-OA
51. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA*. 2014;311(19):1998-2006. doi:10.1001/jama.2014.3741
52. Frampton GM, Fichtenholtz A, Otto GA, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. *Nat Biotechnol*. 2013;31(11):1023-1031. doi:10.1038/nbt.2696
53. Schwarze K, Buchanan J, Taylor JC, Wordsworth S. Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. *Genet Med*. 2018;20(10):1122-1130. doi:10.1038/gim.2017.247
54. Bewicke-Copley F, Arjun Kumar E, Palladino G, Korfi K, Wang J. Applications and analysis of targeted genomic sequencing in cancer studies. *Comput Struct Biotechnol J*. 2019;17:1348-1359. doi:10.1016/j.csbj.2019.10.004
55. Drilon A, Wang L, Arcila ME, et al. Broad, hybrid capture-based next-generation sequencing identifies actionable genomic alterations in lung adenocarcinomas otherwise negative for such alterations by other genomic testing approaches. *Clin Cancer Res*. 2015;21(16):3631-3639. doi:10.1158/1078-0432.Ccr-14-2683
56. Presley CJ, Tang D, Soulos PR, et al. Association of broad-based genomic sequencing with survival among patients with advanced non-small cell lung cancer in the community oncology setting. *JAMA*. 2018;320(5):469-477. doi:10.1001/jama.2018.9824
57. Phillips KA, Deverka PA, Marshall DA, et al. Methodological issues in assessing the economic value of next-generation sequencing tests: many challenges and not enough solutions. *Value Health*. 2018;21(9):1033-1042. doi:10.1016/j.jval.2018.06.017
58. Pennell NA, Mutebi A, Zhou ZY, et al. Economic impact of next-generation sequencing versus single-gene testing to detect

genomic alterations in metastatic non–small-cell lung cancer using a decision analytic model. *JCO Precis Oncol*. 2019;3:1-9. doi:10.1200/po.18.00356
59. Barlesi F, Mazieres J, Merlio JP, et al. Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT). *Lancet*. 2016;387(10026):1415-1426. doi:10.1016/s0140-6736(16)00004-0
60. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361(10):947-957. doi:10.1056/NEJMoa0810699
61. Oshima Y, Tanimoto T, Yuji K, Tojo A. EGFR-TKI-associated interstitial pneumonitis in nivolumab-treated patients with non-small cell lung cancer. *JAMA Oncol*. 2018;4(8):1112-1115. doi:10.1001/jamaoncol.2017.4526
62. Pichler T, Rohrmoser A, Letsch A, et al. Information, communication, and cancer patients' trust in the physician: what challenges do we have to face in an era of precision cancer medicine? *Support Care Cancer*. 2021;29(4):2171-2178. doi:10.1007/s00520-020-05692-7
63. Aggarwal C, Rolfo CD, Oxnard GR, Gray JE, Sholl LM, Gandara DR. Strategies for the successful implementation of plasma-based NSCLC genotyping in clinical practice. *Nat Rev Clin Oncol*. 2021;18(1):65-62.
64. Rolfo C, Mack P, Scagliotti GV, et al. Liquid biopsy for advanced NSCLC: a consensus statement from the International Association for the Study of Lung Cancer. *J Thorac Oncol*. 2021;16(10):1647-1662. doi:10.1016/j.jtho.2021.06.017
65. Merker JD, Oxnard GR, Compton C, et al. Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists joint review. *J Clin Oncol*. 2018;36(16):1631-1641. doi:10.1200/jco.2017.76.8671
66. Cheema PK, Menjak IB, Winterton-Perks Z, et al. Impact of reflex *EGFR/ALK* testing on time to treatment of patients with advanced nonsquamous non–small-cell lung cancer. *J Oncol Pract*. 2017/02/01 2016;13(2):e130-e138. doi:10.1200/JOP.2016.014019
67. Anand K, Phung TL, Bernicker EH, Cagle PT, Olsen RJ, Thomas JS. Clinical utility of reflex ordered testing for molecular biomarkers in lung adenocarcinoma. *Clin Lung Cancer*. 2020;21(5):437-442. doi:10.1016/j.cllc.2020.05.007
68. Weipert CM, Ryan KA, Everett JN, et al. Physician experiences and understanding of genomic sequencing in oncology. *J Genet Couns*. 2018;27(1):187-196. doi:10.1007/s10897-017-0134-3
69. Hirsch FR, Kerr KM, Bunn PA Jr, et al. Molecular and immune biomarker testing in squamous-cell lung cancer: effect of current and future therapies and technologies. *Clin Lung Cancer*. 2018;19(4):331-339. doi:10.1016/j.cllc.2018.03.014
70. VanderWalde A, Grothey A, Vaena D, et al. Establishment of a molecular tumor board (MTB) and uptake of recommendations in a community setting. *J Pers Med*. 2020;27(4):252. doi:10.3390/jpm10040252
71. Centers for Medicare & Medicaid Services (CMS). Department of Health and Human Services. Medicare Program: Hospital Outpatient Prospective Payment and Ambulatory Surgical Center Payment Systems and Quality Reporting Programs. *Final rule with comment period. Fed Regist*. 2017;82(217):52356-52637.
72. Centers for Medicare & Medicaid Services (CMS). *Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450N)*. CMS; 2018.
73. Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet*. 2021;398(10308):1344-1357. doi:10.1016/s0140-6736(21)02098-5
74. Spicer J, Wang C, Tanaka F, et al. Surgical outcomes from the phase 3 CheckMate 816 trial: nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo alone as neoadjuvant treatment for patients with resectable non-small cell lung cancer (NSCLC) [abstract]. *J Clin Oncol*. 2021;39(15 suppl I):8503. doi:10.1200/JCO.2021.39.15_suppl.8503

How to cite this article: Fox AH, Osarogiagbon RU, Farjah F, et al. The American Cancer Society National Lung Cancer Roundtable strategic plan: advancing comprehensive biomarker testing in non–small cell lung cancer. *Cancer*. 2024;130(24):4188-4199. doi:10.1002/cncr.34628