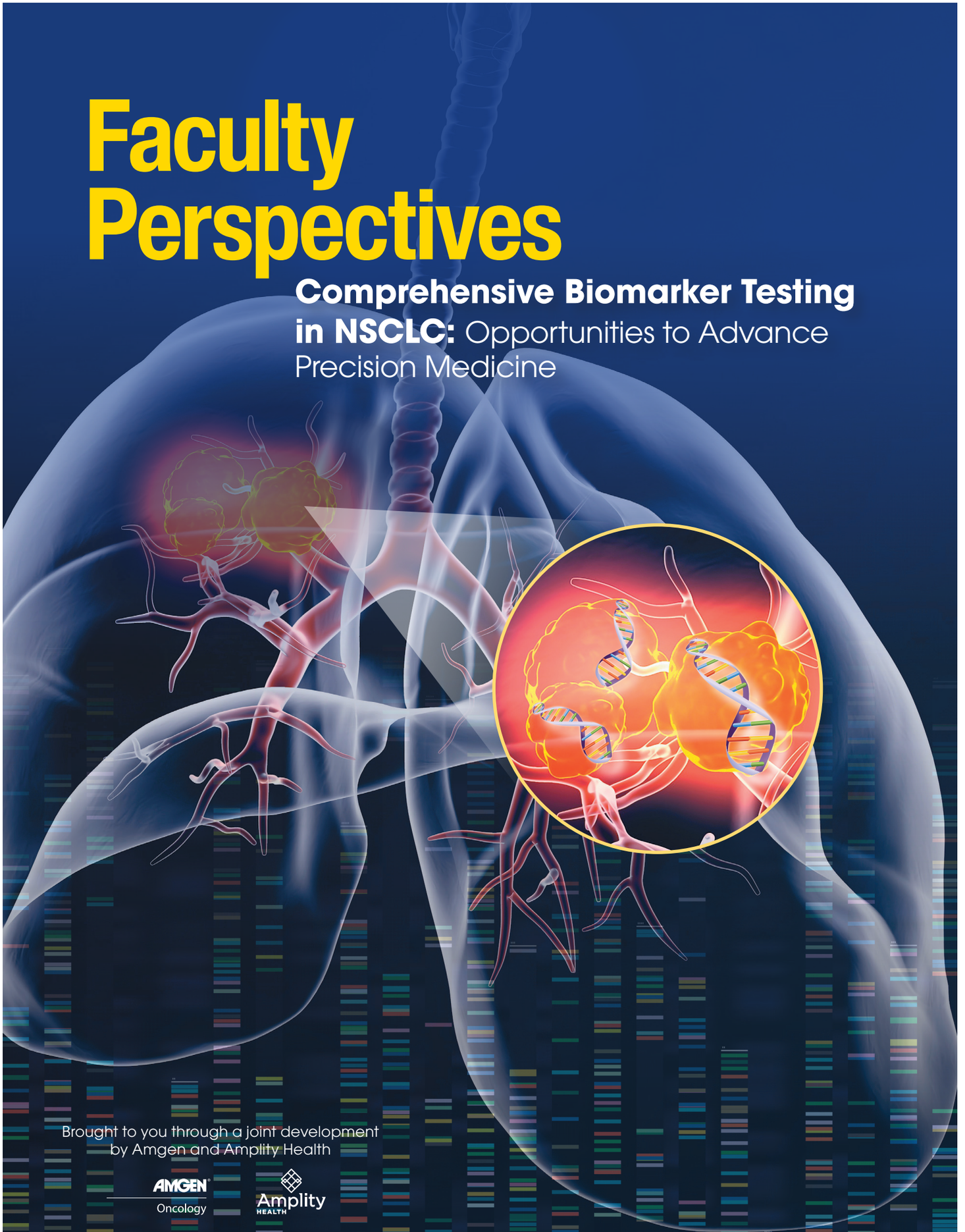
Faculty Perspectives

Comprehensive Biomarker Testing in NSCLC: Opportunities to Advance Precision Medicine



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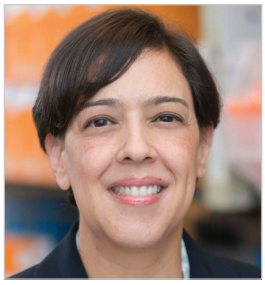
For this supplement, expert faculty provided detailed perspectives based on their extensive experience in the management of non–small-cell lung cancer (NSCLC), focusing on the incorporation and considerations for biomarker testing in precision medicine.



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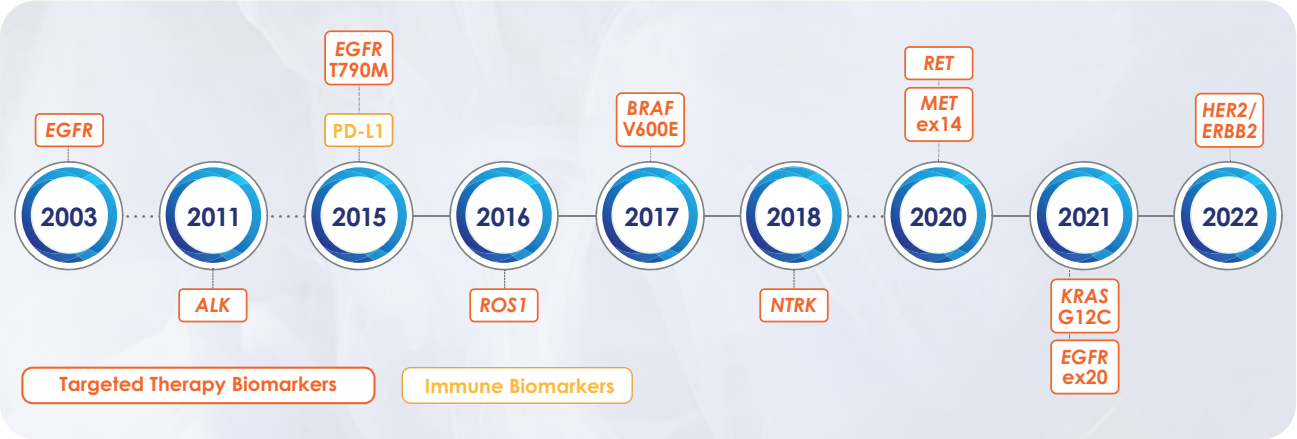
The evolving landscape of actionable biomarkers in NSCLC[1,2]



Which biomarkers do you typically test for in your practice?

DR. SOCINSKI – *We have a comprehensive 51-gene panel that covers all of the currently actionable molecular biomarkers:* EGFR, ALK, ROS1, BRAF, NTRK, METex14, RET, KRAS G12C, *and* HER2. *We also test for* PD-L1 *expression using immunohistochemistry.*[3,4]

MS. WELCH – *We try to get full next-generation sequencing (NGS) of hundreds of genes on all of our patients with metastatic lung cancer.*[3,4]

DR. ARCILA – *We have a comprehensive NGS panel that tests 505 genes. We also have rapid screening assays for common mutations in* EGFR *and* KRAS *and for fusions.*[3,4]

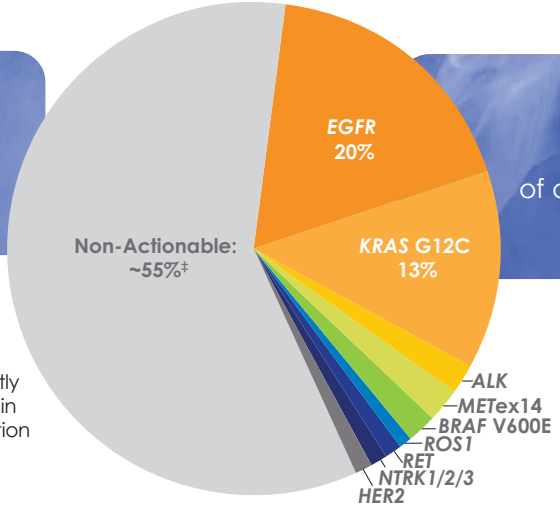
Consider a broad-based biomarker testing approach in order to identify actionable as well as emerging driver mutations, which may open the path for more treatment plans[5]

Prevalence of oncogenic drivers in NSCLC[6]

~45%* patients with nonsquamous NSCLC have an actionable driver mutation[3,5†]

*12.4% (KRAS G12C) + 20.4% (EGFR) + 1.7% (EGFR exon20) + 1.9% (ALK) + 1% (ROS1) + 1.6% (BRAF V600E) + 2.4% (MET) + 0.9% (RET) + 0.1% (NTRK) + 2.2% (HER2) = 44.6% or ~45%

†Molecular alteration prevalence can vary slightly between different datasets and studies. Values in graph based on approximate molecular alteration frequencies from the AACR genie version 12.0 dataset (N = 19,777). Participating institutions include academic centers in western countries. This graph only includes alterations predictive of response to an FDA-approved drug in locally advanced or metastatic NSCLC.[5]



‡100% - 45% actionable driver mutations = 55% non-actionable driver mutations

KRAS G12C and *EGFR* make up **~75%§** of all actionable drivers in nonsquamous NSCLC[3,5]

§12.4% (KRAS GC12C) + 20.4% (EGFR) + 1.7% (EGFR exon20)/ 45% = 76.7% or ~75%

Integrating biomarker testing into clinical practice

DR. ARCILA – *We perform testing by NGS at diagnosis and upon progression/relapse. Some NGS assays may also be performed for monitoring of disease during the course of treatment.*[5]

MS. WELCH – *In my cancer center, comprehensive NGS testing is done at diagnosis, sometimes with both plasma and tissue to expedite results. NGS testing is repeated at the time of progression.*[7]

DR. SOCINSKI – *We typically do biomarker testing at lung cancer diagnosis but retesting at progression can also be therapeutically informative. By retesting, you may find a different actionable mutation that may help inform the patient's treatment plan.*[7]

It is advisable to test for actionable and emerging biomarkers in eligible patients with advanced NSCLC at diagnosis and during the course of the disease[5,8,9]

Recent data show that <50% of eligible patients with NSCLC receive biomarker testing

A retrospective, observational study conducted in the community setting revealed that approximately half of the 2257 eligible patients with metastatic NSCLC received a biomarker test result prior to first-line treatment for the biomarkers available at the time (*ALK, EGFR, BRAF, ROS1,* or *PD-L1*).[10] Another community-based retrospective study examining biomarker testing patterns among 3474 patients diagnosed with metastatic NSCLC showed 46% of patients received comprehensive biomarker testing for *ALK, EGFR, BRAF, ROS1,* and *PD-L1* at any time.[11]

This retrospective observational study utilized a database to obtain data of 23,488 patients with advanced/metastatic NSCLC, breast, and colorectal cancer. At the time of analysis, the advanced/metastatic NSCLC database was limited to evaluating NGS-based tests for *ALK, EGFR, ROS1, KRAS,* and *BRAF*. In the nonsquamous NSCLC cohort (n = 10,333), White patients were more likely (36.6%) to receive NGS testing than Black patients (29.7%) before first-line therapy ($P < 0.0001$) and at any given time (54.7% vs 43.8%, $P < 0.0001$).[12]

Guidelines recommend broad molecular testing for eligible patients with advanced NSCLC[3,4,8,13]

Guideline	Panel type	Biomarker tested
NCCN v2.2023	Single-gene or expanded panel	*EGFR, ALK, PD-L1, ROS1, BRAF, NTRK, MET, RET, KRAS, HER2*
ASCO 2018, 2022	Single-gene or expanded panel	*EGFR, ALK, ROS1, BRAF, MET, RET, KRAS, HER2*
CAP/IASLC/AMP 2018	Single-gene or expanded panel	*EGFR, ALK, ROS1, BRAF, MET, RET, KRAS, HER2*

Adherence to testing for guideline-recommended biomarkers, regardless of therapy, has significantly decreased mortality risk by 11%[14*]

ASCO, American Society of Clinical Oncology; CAP/IASLC/AMP, College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology; NCCN, National Comprehensive Cancer Network.

***Retrospective study of 28,784 adult patients diagnosed with advanced NSCLC from January 1, 2011 through July 31, 2019 obtained data from a real-world database to assess the association between adherence to NCCN recommendations for biomarker testing and overall survival. The testing-adherent group (n = 19,787) consisted of patients with evidence of testing for any biomarkers including *EGFR, ALK, BRAF, KRAS, ROS1,* or *PD-L1* between 14 days prior to and 90 days after diagnosis. The study showed an 11% decreased mortality risk; hazard ratio = 0.89, 95% confidence interval 0.86, 0.92; $P<0.01$.[14]**

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Integrating biomarker testing into clinical practice... *continued from page 4*

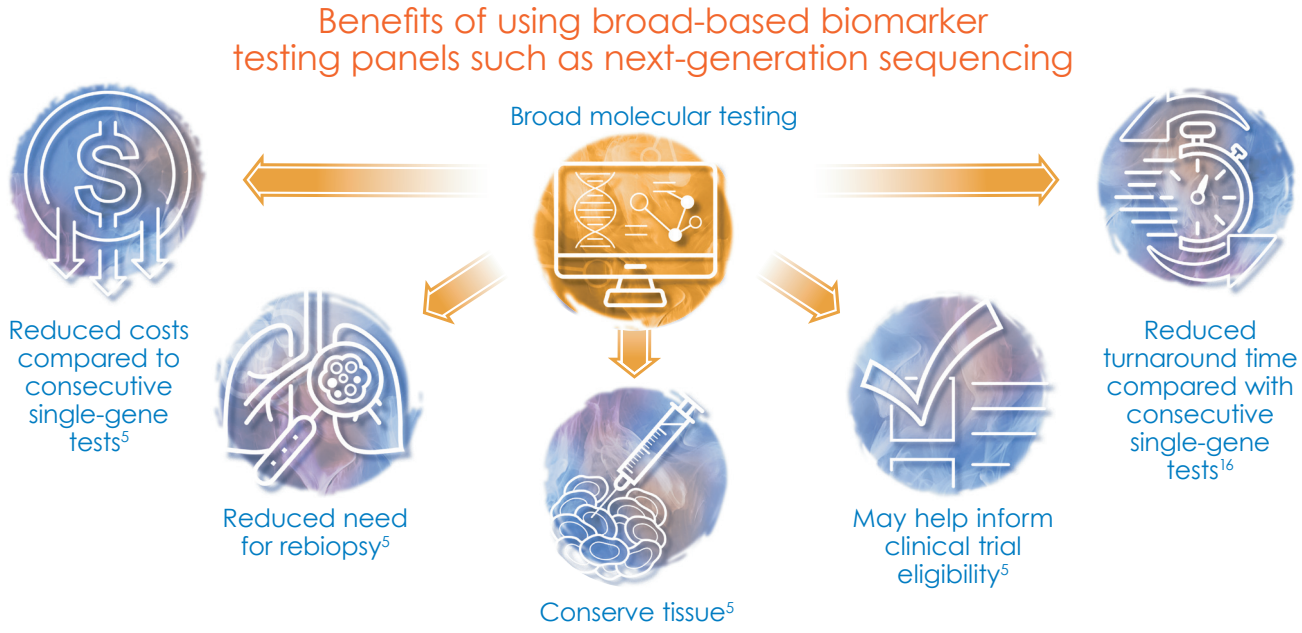
What has been the impact of integrating biomarker testing in routine clinical practice?

MS. WELCH – *By routinely incorporating biomarker testing in appropriate patients, we get a better understanding of what may be driving these patients' cancers.*[7]

DR. ARCILA – *The overall survival of patients with lung cancer has increased in the past decade primarily because of personalized treatment plans.*[14,15]

Considerations for optimizing the biomarker testing journey in NSCLC

A. Broad molecular testing identifies actionable biomarkers in either a single assay or a combination of a few assays, and optimally also identifies emerging biomarkers[3]



What is the impact of broad-based multigene biomarker testing on clinical workflow compared with single-gene testing?

DR. SOCINSKI – *Many of the biopsies in my lung cancer practice are technically difficult to obtain and you may not get bountiful tissue in the biopsy. Our patients are better served if we get all the information we need upfront with broad molecular testing and do not have to go back and subject the patient to a second biopsy using single-gene testing.*[5]

DR. ARCILA – *Next-generation sequencing technology enables comprehensive simultaneous screening for all required markers, decreasing overall cumulative costs, number of personnel, and patient sample requirements, compared to single-gene testing.*[5] *The more comprehensive assays tend to be highly complex resulting in a longer turnaround time.*[5] *An equally critical issue is that more comprehensive assays require a team of specialists to handle the breadth and depth of the biomarker information.*[5]

Broad multigene testing can reduce the number of order assays and conserve tissue needed to assess all actionable biomarkers[5]

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Considerations for optimizing the biomarker testing journey... *continued from page 5*

B. In reflex biomarker testing, the pathologist orders a group of preapproved biomarkers at the time of initial diagnosis[17]

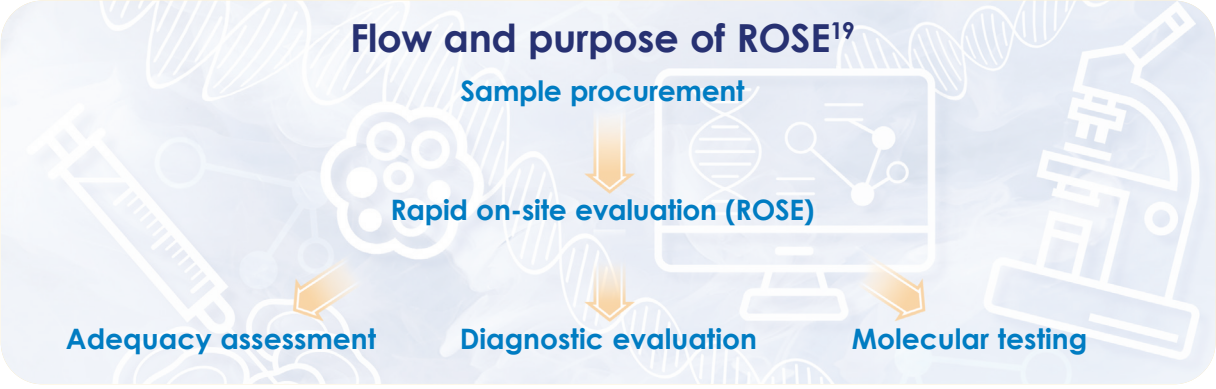
- **Considerations for implementing reflex testing protocols[17]**
  - Reduces the time from lung cancer diagnosis to delivery of all clinically actionable results
  - Decreases turnaround time of molecular testing results
  - Improves detection rate of targeted gene alterations

What impact does reflex testing have on patient care?

DR. SOCINSKI **–** *At our center, the reflex biomarker testing occurs, for example, with the initial biopsy at the time of diagnosis. The major benefit of reflex testing is that it allows the clock to start earlier.*[18] *We have all these targeted therapies and various immunotherapeutic approaches, and we want to select the most appropriate treatment option quickly to be most beneficial for patients.*[18]

MS. WELCH **–** *In my experience, the greatest benefit from the medical oncology side with reflex testing is that by the time we meet the patient, we often already have the results, so we are able to make a treatment plan and thus avoid a delay in care.*[18]

C. Rapid on-site evaluation (ROSE) is performed to increase tissue sample adequacy rate and diagnostic yield to help reduce rebiopsy rates. ROSE quickly guides appropriate sampling for molecular testing and provides a preliminary diagnosis to help direct immediate patient care[19]



What impact has ROSE had on clinical workflow efficiencies?

DR. ARCILA **–** *Changes to our comprehensive quality assurance program in the way that we obtain, handle, and process the biopsies and the way that they are evaluated upfront increased our success rate of obtaining an adequate amount of tissue from approximately 75% to approximately 90%.*[20-22]

Implementation of ROSE led to 15% increase in success rate of obtaining adequate amount of tissue[20-22]

The pathology group at Memorial Sloan Kettering conducted a retrospective review of EBUS-TBNA from March 1, 2014 - September 14, 2016 to determine whether EBUS-TBNA could reliably provide sufficient material for large hybrid capture NGS. A total of 784 EBUS-TBNA procedures were performed during the study period. The success rate in earliest one-third of cases was 76.3% vs 92.3% in the most recent third of cases. This improved success rate may be attributed to the development and implementation of refinements in EBUS-TBNA technique, increased experience with ROSE in the operating room, the evolution of DNA extraction techniques, and modification of the cell block preparation technique, resulting in better tissue acquisition.[22]

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Considerations for optimizing the biomarker testing journey... *continued from page 6*

DR. SOCINSKI – *ROSE may improve workflow efficiency because the on-site pathologist can take a quick look and make sure that the clinician taking the biopsy (eg, the thoracic surgeon or interventional pulmonologist) has hit the target.*[19] *This may increase efficiency, but it may also increase cost because not only do you have the person doing the biopsy, but additionally the pathologist and the related infrastructure necessary to perform ROSE.*[19]

MS. WELCH – *ROSE does add an additional layer of multidisciplinary coordination: it is necessary to have a cytopathologist or a similar clinician to evaluate the tissue.*[19] *We have to coordinate these various roles at the same time that the interventional radiologists and surgeons are performing the biopsies.*[18]

ROSE can help attain adequate tumor sample for molecular biomarker testing[18]

D. Liquid biopsy uses DNA shed from tumors into the circulation as a substrate for molecular biomarker testing.[7,18] Although tumor tissue remains the gold standard for molecular analyses, liquid biopsy may be considered a key element in comprehensive testing when tissue-based testing is inadequate[18]

- **Considerations for liquid biopsy**

  Pros
  - Liquid biopsy can be used when the tissue specimen is insufficient or of low quality for biomarker testing[18]
  - Liquid biopsy is less invasive and shortens turnaround time[7]
  - Liquid biopsy testing can be serially performed to follow treatment response and identify development of acquired resistance before observance of radiographic or clinical progression[5]
  - Compared with tissue-based testing, liquid biopsy can better reflect the systemic tumor burden and intratumoral heterogeneity[7]
  - Results based on liquid biopsy can complement tissue studies[7]

  Cons
  - Not all tumors shed sufficient DNA for detection[18]
  - Negative test by liquid biopsy requires confirmation using tissue biopsy[24]

When might it be appropriate to consider liquid biopsy for biomarker testing, as well as its advantages and disadvantages?

DR. SOCINSKI – *I consider obtaining a plasma based biopsy almost every time I run biomarker tests, and I base that on evidence from a couple of studies. A study of 323 enrolled patients found that the addition of liquid-biopsy testing to tissue-biopsy testing increased the detection rate of an actionable mutation from 20.5% to 35.8%.*[25] *In addition to confirming these findings, a different study of 282 patients demonstrated that liquid-biopsy testing successfully identified actionable mutations at a rate similar to tissue-based testing.*[23]

MS. WELCH – *In my opinion, it is always appropriate to consider liquid biopsy for biomarker testing; it has a much quicker turnaround time than tissue biopsy.*[7] *Another advantage to liquid biopsy is that it may provide a broader reflection of the mutations that may be driving cancer growth.*[7] *On the other hand, it is harder for liquid biopsies to pick up fusion mutations.*[7]

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Considerations for optimizing the biomarker testing journey... *continued from page 7*

DR. ARCILA – *The liquid biopsy is minimally invasive and enables detection of genetic biomarkers when a biopsy is not possible. The 3 main drawbacks of liquid biopsy testing are: First, it may be less sensitive compared to tissue particularly for tumors that have a low-shedding of circulating tumor DNA.[7] This means a negative result should be considered a false-negative until proven otherwise, and it should be followed up with a tissue biopsy.[24] Second, may have low specificity since a liquid biopsy captures DNA from all body sites and the origin cannot be determined from the DNA sequence alone. Lastly, both malignant and premalignant conditions from hematopoietic cells may be detected in the liquid biopsy and may complicate interpretations.[7]*

Concurrent use of liquid and tissue biopsy can increase detection of actionable and emerging biomarkers[7,25]

E. Multidisciplinary team (MDT) collaboration may support patient care through early initiation of a treament plan[18]

How has the collaboration between members of the MDT enhanced patient care?

DR. SOCINSKI – *In 1995 I was hired at the University of North Carolina to start their MDT, which brought a team of a medical oncologist, the pulmonologist, thoracic surgeons, and radiation oncologists together with nurse navigation to start the multidisciplinary thoracic program. I can tell you I am such a better medical oncologist because of what I've learned from pulmonologists, surgeons, radiation oncologists, because they have a different perspective.*

I think at the end of the day, patients who go through a multidisciplinary approach end up having a treatment plan initiated earlier than when a multidisciplinary strategy is not implemented.[18,26]

MS. WELCH – *In my practice, advanced practice providers are very involved in the biomarker testing process and in assisting with ordering the tests. Often, we take on the role of explaining to patients the importance of biomarker testing, the testing process, and the significance of the results.*[27,28]

F. Standardized methods to document biomarker test results may facilitate future access as needed[29,30]

- Considerations for Consistent Reporting and Documenting
  - Include all actionable mutations at the beginning of the report[29]
  - Report all mutations at the variant level[29]
  - Use uniform and unambiguous nomenclature to report variants (ie, *KRAS* G12C)[29]
- Retrieving Biomarker Results
  - Store patients' biomarker test reports in a reliable location in their EMR, such as in your notes or their chart[30]
  - Consider establishing the optimal location for test results with your multidisciplinary team for easy retrieval by providers, now and in the future[30]

What processes do you have in place at your institution to document and integrate precision medicine information, for easy access of results at diagnosis and upon progression?

MS. WELCH – *At our large community-based practice, we have a database platform that houses all of molecular testing results for our entire practice. This makes interrogating for specific mutations relatively easy to identify patients with specific genomic drivers.[30] Next-generation sequencing reports are annotated in the electronic health record[29] and molecular testing results are pulled forward into the patient's notes. Many providers list NGS and PD-L1 results in the molecular profiling section of the Assessment/Plan. When a patient progresses, molecular testing is repeated and results are reviewed to help direct the next steps in patient care.*[7]

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Considerations for optimizing the biomarker testing journey... *continued from page 8*

DR. SOCINSKI **–** *In the lung cancer program at Advent Health, we have many processes in place to help ensure no actionable biomarker is missed at disease progression. It starts with our navigators who keep a pretty close eye on our lung cancer patients. They send the pathology and molecular testing reports via e-mail to the oncologist. Secondly, we have a weekly thoracic tumor board and a biweekly molecular board where biomarker testing of our lung cancer patients is discussed.*[30] *Lastly, operationally, the biomarker testing results are automatically uploaded into Epic, then into my inbox for review, and finally into the electronic medical record report.*[29] *Details of the biomarker testing results are recorded in the pathology section of Epic for example: Molecular tests show KRAS G12C status, PD-L1 expression levels, etc.*[29] *These multiple procedures work well at our cancer center to ensure that results are properly documented and easily accessible by all treating physicians on the case at different lines of therapy.*

DR. ARCILA **–** *In our practice, our team developed and implemented a clinical variants results system. Following data analysis, variant results are stored in this system. A web user interface allows the users to access and interact with the content for review and generation of reports.*[30] *The system also enables tracking of all biomarker test results from the time of initial diagnosis and across any other timepoint at which testing is done. Variants are annotated based on highly curated evidence, including the ranking for the level of evidence that a specific molecular alteration is predictive of drug response by FDA labeling and NCCN guidelines. Molecular testing reports are accessible through the EMR,*[29] *along with all other pathology reports.* ■

Ensuring genomic test results are consistently reported and documented and easily retrievable may facilitate accessibility to results when necessary[29,30]

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