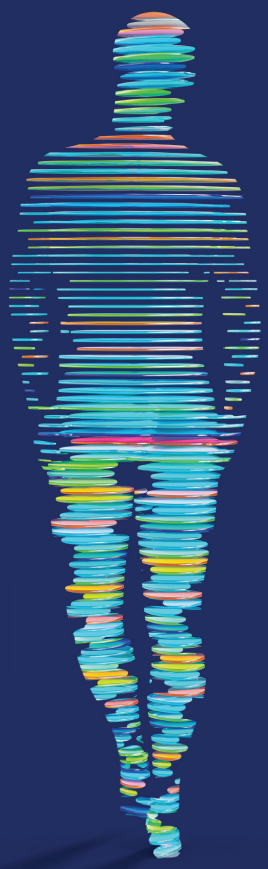
The Importance of a Molecular Diagnosis in mNSCLC

Understanding the essential role of biomarker testing in patient care



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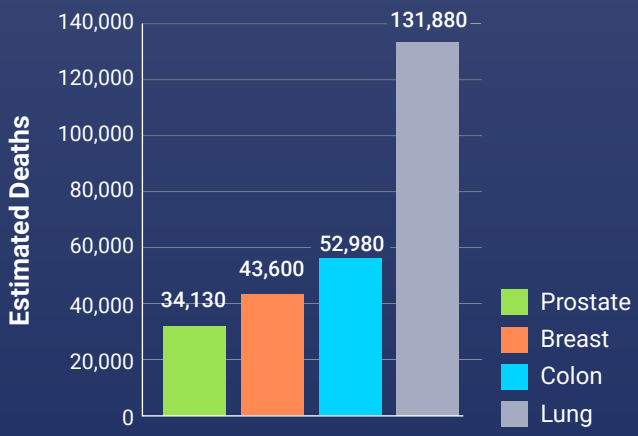
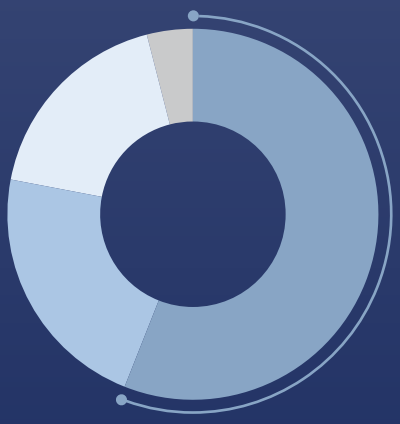
LUNG CANCER OVERVIEW

Lung cancer is the leading cause of cancer-related mortality, and most patients receive a diagnosis of metastatic disease[1]

Estimated Mortality in 2020[1]



Stage at Diagnosis[1]



56%
of patients with lung cancer have **metastatic disease** at diagnosis

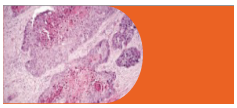
Unknown
Localized
Regional
Metastatic

85% of patients with lung cancer are diagnosed with NSCLC[2]

HISTOLOGIC SUBTYPES OF NSCLC

NSCLC Histologic Subtypes[2,3]

Adenocarcinoma
≈78%



Squamous Cell Carcinoma
≈18%

Other*
≈4% (pictured: large cell carcinoma)

**Includes large cell carcinoma, adenosquamous carcinoma, and others.*

While histology began to guide therapeutic decisions in the early 2000s, molecular subtypes have gained importance in clinical decision-making[2,4-11]

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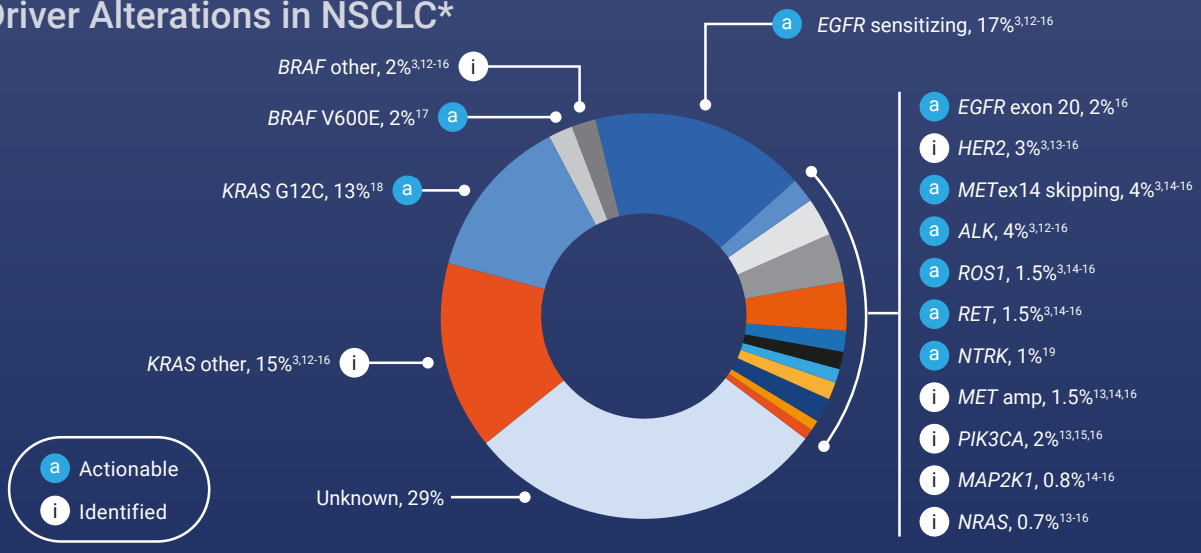
MOLECULAR SUBTYPES OF NSCLC

More than 15 driver alterations have been identified since 2004; these are often mutually exclusive

Driver Alterations in NSCLC*



9 driver alterations have an associated FDA-approved therapy as of June 2021[20]

≈50%
of patients with mNSCLC have an actionable driver[2,3,12-21]

≈20%
of patients with mNSCLC harbor 1 of the 6 less common actionable alterations[2,3,12-21,†]

Per guidelines, the genomic complexity of NSCLC calls for broad molecular profiling to detect actionable biomarkers in eligible patients[22-24]

**Prevalence rates are an average from 6 studies including a total of 8,533 patients and are in accordance with those from The Cancer Genome Atlas (TCGA) Research Network, a joint effort between the National Cancer Institute and the National Human Genome Research Institute. To access the latest TCGA data, please visit: cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga. Please see the appendix to this presentation for the calculations.*
†Less common actionable alterations affect <5% of patients with mNSCLC.

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MOLECULAR DIAGNOSTICS

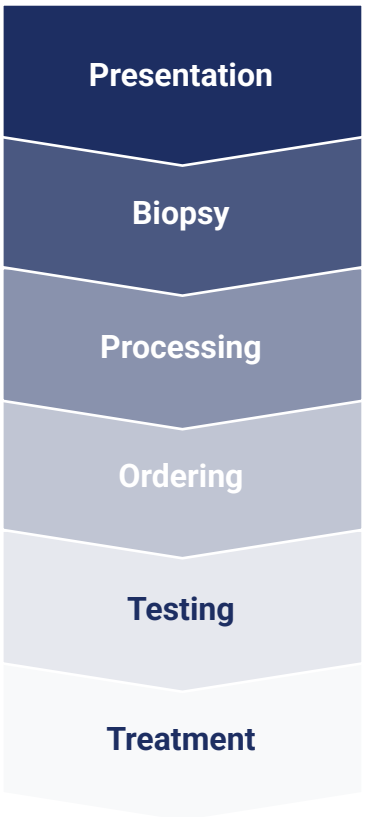
The Multidisciplinary Team (MDT)

Molecular diagnostics is a multistep process requiring collaboration among distinct disciplines[25]

MDT Roles in the Diagnostic Journey for Patients With mNSCLC

Testing Navigation

Monitoring and managing as done by the **nurse and other medical professionals**[25]



Oncologist orders imaging and diagnostic tests after patient presents with suspected mNSCLC[26]

Interventionalist collects tissue or blood sample with potential input from **pathologist** to confirm sufficiency during biopsy via ROSE[25,26]

Laboratory staff prepare sample for testing under **pathologist** supervision who may identify best tissue for subsequent testing[25,26]

The **oncologist**, **pulmonologist/ interventionalist,** and/or **pathologist** may order biomarker testing[25]

Pathologist interprets result(s) and prepares a report after performing testing, with assistance from **laboratory staff**[25]

Oncologist may use biomarker test results to make treatment decisions. **Pathologist** may be consulted for test interpretation[25,26]

Problems at Any Step in the Diagnostic Process May Negatively Impact Patient Care

GUIDELINE RECOMMENDATIONS

Guidelines recommend biomarker testing at initial diagnosis of mNSCLC

2022 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[22,*]

Test all eligible patients up front for:

EGFR	*ALK*
ROS1	*BRAF*
NTRK1/2/3	*RET*
*MET*ex14 skipping	*KRAS*
PD-L1	

NCCN Guidelines (Oncology Guidelines) are evidence- and consensus-based guidelines that are updated continually, with at least 1 update per year[27]

2018 CAP-IASLC-AMP Guidelines[23]

Test all patients for:

EGFR	*ALK*	*ROS1*

Test as part of a broad panel:

BRAF	*RET*	*HER2*
KRAS	*MET*ex14 skipping	

Test for†:

PD-L1

CAP-IASLC-AMP Guidelines (Pathology Guidelines) are evidence-based guidelines[23]

- The next update for the CAP-IASLC-AMP Guidelines is in development and expected in 2023[23,28]

***BRAF*, *NTRK1/2/3*, *RET*, *MET*ex14 skipping, and *KRAS* have all become actionable since the last update of the CAP-IASLC-AMP Guidelines[2,20,23]**

**The NCCN Guidelines for NSCLC provide recommendations for certain individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays or commercial laboratories.*
†*Opinion; subject of upcoming guideline.*

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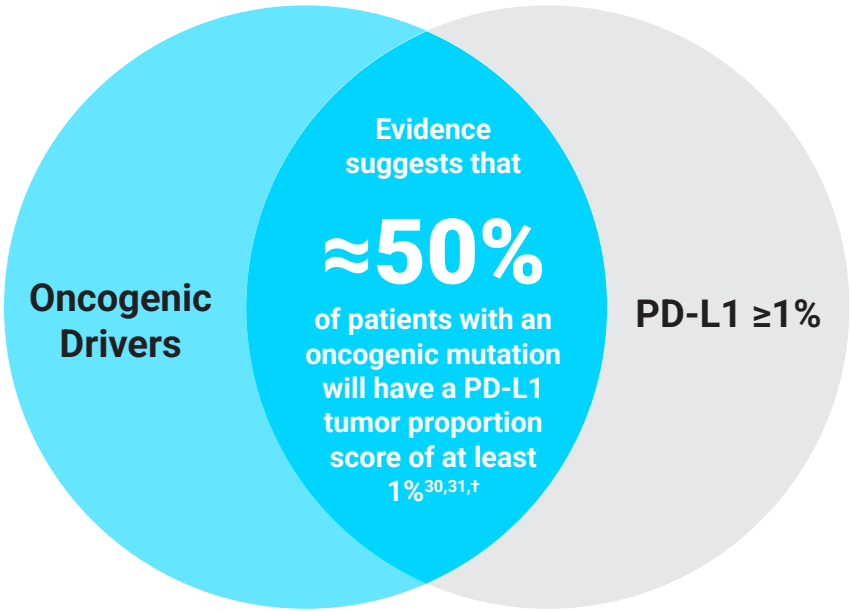
GUIDELINE RECOMMENDATIONS (CONTINUED)

> The NCCN NSCLC Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available"[22,*]

> The NCCN NSCLC Panel recommends that clinicians should obtain molecular testing results for actionable biomarkers before administering first-line ICI therapy, if clinically feasible, including *ALK, BRAF, EGFR*, *MET*ex14 skipping, *NTRK1/2/3*, *RET*, and *ROS1* variants"[22]

An independent retrospective analysis examining the impact of adherence to NCCN Guidelines for testing suggests patients with mNSCLC who receive NCCN Guidelines adherent care had improved outcomes[29]



Importantly, oncogenic drivers are often mutually exclusive, but **the presence of an oncogenic driver is not mutually exclusive with elevated PD-L1 expression**[30-33]

**Broad molecular profiling is defined as molecular testing that identified all (NCCN recommended) biomarkers in either a single assay or a combination of a limited number of assays.*

[†]Based on 2 separate analyses: 1) a prospective analysis conducted in ≈10,000 patients analyzing PD-L1 TPS ≥1% and EGFR, ALK, or KRAS; and 2) a multicenter, registrational study of 214 patients analyzing PD-L1 TPS of 1% and HER2, EGFR, ALK, KRAS, RET, MET, BRAF, or ROS1.

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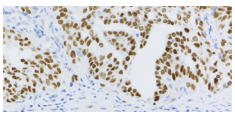
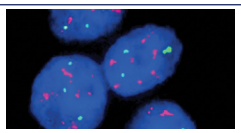
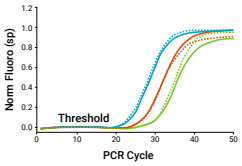
TISSUE REQUIREMENTS FOR BIOMARKER TESTING

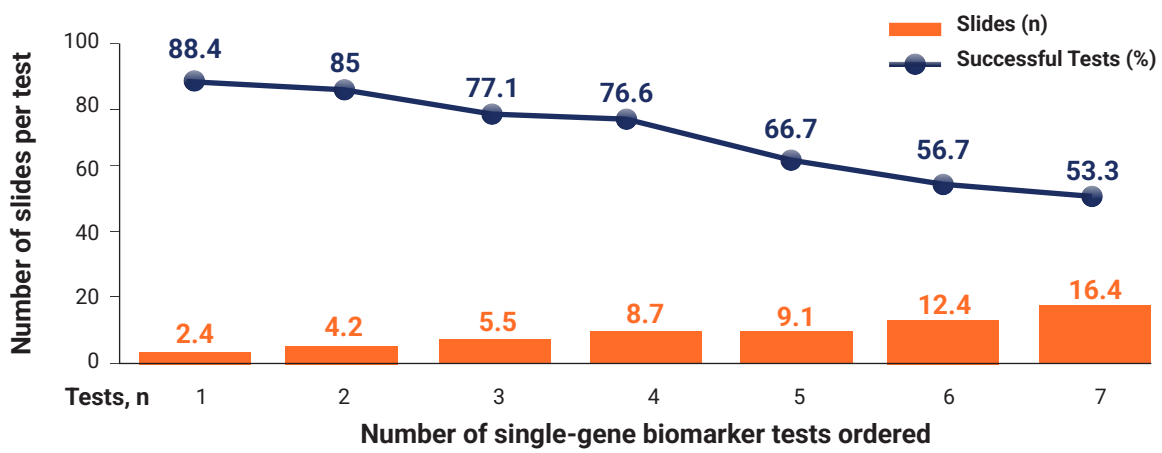
Biopsies may not provide enough tissue to test all biomarkers by single-gene testing approaches

Single-gene testing[20]		Can assess[20]	Biomarkers tested[22,23]	Tissue[20,34-36]
IHC		Protein expression	*ALK, NTRK, PD-L1, ROS1,*	≥100 tumor cells
FISH		Rearrangements, CNVs	*ALK, MET amplification, NTRK, RET, ROS1,*	≥50 tumor cells
RT-PCR		SNVs, indels, known rearrangements	*BRAF V600E, EGFR, KRAS G12C* *While ALK, NTRK, RET, and ROS1 can be detected with targeted RT-PCR assays, these assays are unable to detect novel fusion partners*	≥5% tumor cells

Intended to depict biomarker testing methodologies. When testing for therapy selection, please consult product prescribing information and FDA-approved companion diagnostics.

Images adapted from Yu J et al. *Sci Rep.* 2019;9(1):7518, Yatabe Y et al. *J Thorac Oncol.* 2019;14(3):377-407, and Kipf E et al. *J Mol Diagn.* 2022;24(1):57-68.

Slide Consumption and Testing Success Rates With Single-Gene Tests[37]



With sequential single-gene testing, ≈50% of patients will not have successful biomarker testing for >7 biomarkers[37]

In a survey, 1 in 3 US oncologists report that inadequate tumor specimens are a barrier to biomarker testing, so obtaining sufficient tissue for biomarker testing during biopsy is critical[38,39]

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NEXT GENERATION SEQUENCING (NGS)

NGS may overcome some limitations of sequential single-gene testing that may lead to tissue exhaustion

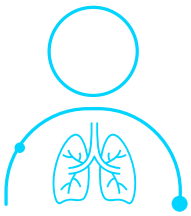
SEQUENTIAL SINGLE-GENE TESTING[37,*]	NGS[37,40,41,†]
8 tests	1 test
8 biomarkers	>50 biomarkers[‡]
17 slides	1-10 slides (≈50-1000 ng DNA)

Intended to depict biomarker testing methodologies. When testing for therapy selection, please consult product prescribing information and FDA-approved companion diagnostics.
*Based on a retrospective study on 1402 samples for single-gene tests done in a large, US-based, Clinical Laboratory Improvement Amendments–certified, commercial reference laboratory from September 2015 to October 2016. †Range is based on the specimen instructions of FoundationOne CDx and a retrospective study on 169 investigational use cases of the Oncomine Dx Target Test done in a large, US-based, Clinical Laboratory Improvement Amendments–certified, commercial reference laboratory from April 2016 to July 2016. Tissue needs vary by assay. ‡Number refers to the number of biomarkers that an NGS assay may be capable of detecting and does not reflect the current number of actionable biomarkers.

NGS assays are not identical[24,37,41-43]

Assays vary by:	The number of biomarkers detected	The types of biomarkers detected	The enrichment method used (specific to targeted assays)	Tissue requirements	Cost

BENEFITS OF NGS



NGS uses
44%-94%
less tissue[37,40,*]

NGS was associated with a
17%-41%
reduction in cost
in a 2017 Medicare study[44,†]

It is important to know what types of alterations your NGS assay can and cannot reliably detect[24]

Intended to depict biomarker testing methodologies. When testing for therapy selection, please consult product prescribing information and FDA-approved companion diagnostics.
*Range is based on the specimen instructions of FoundationOne CDx and a retrospective study on 169 investigational use cases of the Oncomine Dx Target Test done in a large, US-based, Clinical Laboratory Improvement Amendments–certified, commercial reference laboratory from April 2016 to July 2016. Tissue needs vary by assay. †Total testing cost for 2066 Medicare-insured patients in 2017.

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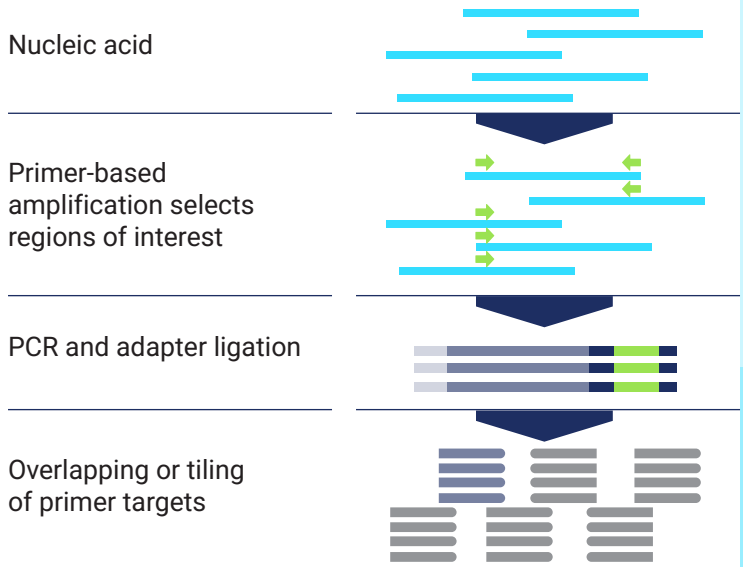
TARGETED NGS ENRICHMENT STRATEGIES

Amplicon-based assays use multiple PCR primers to directly amplify genomic regions of interest[24]

Amplicon-based target enrichment[42]



Pros

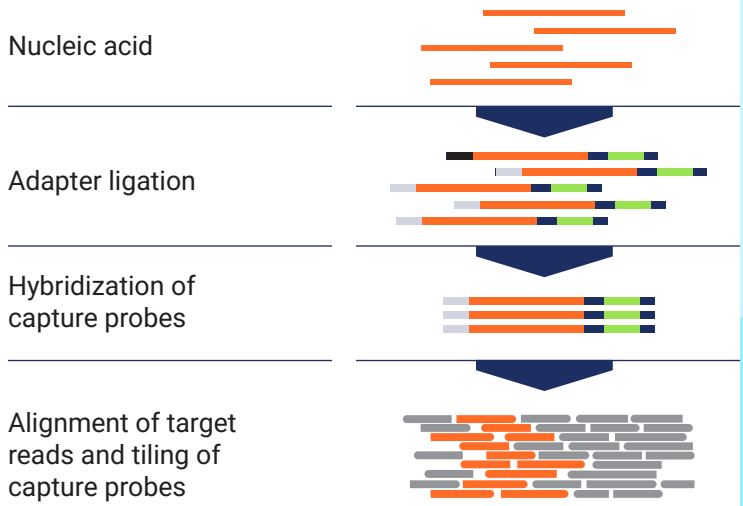
- Efficient for smaller panels[42]
- Can reliably identify point mutations and small indels[24]
- Less nucleic acid required (5-10 ng) and shorter turnaround time (7-10 days) compared to hybrid capture assays[24,42]

Cons

- Cannot reliably detect fusion events or CNVs[24]
- Limitations in the number of genes and regions that can be covered[24]

Hybrid capture-based assays use hybridization to capture large genomic regions and allow a broader assessment of mutations, CNVs, and gene rearrangements incorporated in the panel design[24]

Hybrid capture–based target enrichment[42]



Pros

- Applicable for large assays[40]
- Allow for broader assessment to include CNVs[24]
- Less likely to miss variants[40]
- More uniform and complete coverage[40]

Cons

- Require more nucleic acid (100-200 ng) and longer library preparation and turnaround time (15-20 days) compared with amplicon-based assays[24,42,45]

Image adapted from Church AJ. Next-generation sequencing. In: Tafe L, Arcila M, eds. *Genomic Medicine.* Cham, Switzerland: Springer; 2020:25-40.

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OPTIMIZING BIOPSY SAMPLE ACQUISITION

Societies* recommend several considerations in optimizing sample acquisition during biopsy[46]

Needle Size

- **EBUS-TBNA: 19- to 22-gauge**
- **Transthoracic FNA:** Up to 25 gauge
- **Transthoracic CNB:** Up to 20 gauge

Passes

- **EBUS-TBNA:** 3-5 passes
- **Transthoracic FNA w/o CNB:** Multiple passes enough for a tissue block

Sample Amount/Volume

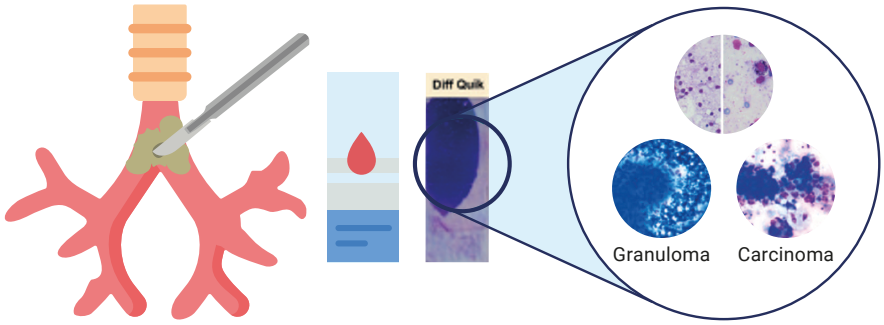
- **Transthoracic CNB:** At least 3 core samples
- As much **pleural fluid** volume as reasonably attainable for cytologic evaluation and ancillary studies

**College of American Pathologists in collaboration with the American College of Chest Physicians, Association for Molecular, American Society of Cytopathology, American Thoracic Society, Pulmonary Pathology Society, Papanicolaou Society of Cytopathology, Society of Interventional Radiology, and Society of Thoracic Radiology.*

RAPID ON-SITE EVALUATION (ROSE)

Multiple societies recommend incorporating ROSE into biopsy procedures[46,*]

ROSE directs the interventionalist in real-time to either acquire more tissue or terminate a sampling procedure once **sufficient material** is acquired[46,47]



An **interventionalist** obtains a tissue specimen, a **cytotechnologist** prepares the slide, and a **cytopathologist** immediately assesses the slide for both adequacy and preliminary diagnosis[46,47]

An MDT is essential in implementing ROSE during tumor biopsy[46]

**Guidelines from the College of American Pathologists in collaboration with the American College of Chest Physicians, Association for Molecular Pathology, American Society of Cytopathology, American Thoracic Society, Pulmonary Pathology Society, Papanicolaou Society of Cytopathology, Society of Interventional Radiology, and Society of Thoracic Radiology.*

Image adapted from Jain D et al. *Arch Pathol Lab Med.* 2018;142:253-262.

TISSUE INSUFFICIENCY

In some patients, NGS of tissue samples may not be possible because of tissue insufficiency. Tissue insufficiency may occur when:

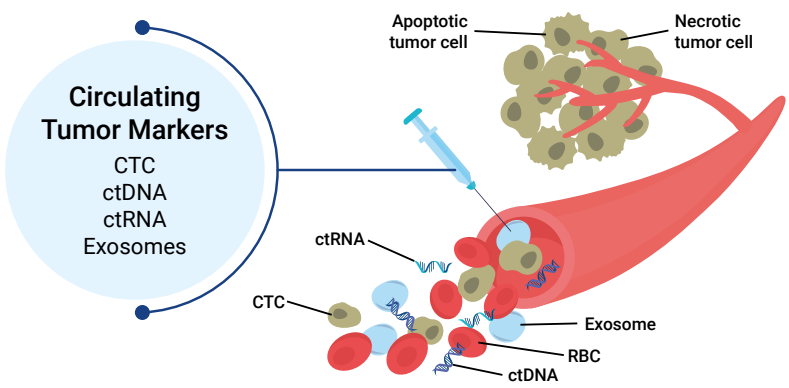
Diagnostic biopsy cannot be obtained[48,49]	Insufficient tissue on initial biopsy[50,51]	Repeat biopsy is not feasible[50]

NCCN recommends that liquid biopsy–based (plasma ctDNA) testing can be considered for eligible patients with mNSCLC in certain specific clinical circumstances[22]

Intended to depict biomarker testing methodologies. When testing for therapy selection, please consult product prescribing information and FDA-approved companion diagnostics.

LIQUID BIOPSY

Different diagnostic tests performed on biological fluids (eg, blood, saliva, urine), with the aim of investigating the presence of CTCs or ctDNA that can be shed from the tumor[52,53]



Key Characteristics of Liquid Biopsy[52,53]

Advantages

- Is minimally invasive
- Can capture tumor genetic heterogeneity and follow subclonal evolution through serial biopsy
- Potentially represents genetic make-up from entire tumor and metastatic sites
- May have a shorter overall turnaround time than tissue-based NGS relative to the date the test is ordered

Disadvantages

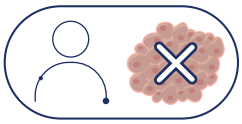
- Cannot directly correlate ctDNA results with histology or cellular phenotype
- Genetic analyses may have biased representation from differential tumor cell turnover
- May be associated with false negatives
- Special processing and handling are required

Image adapted from Qi Z et al. *J Cancer.* 2018;9(18):3417-3426.

IASLC and NCCN Propose 3 Approaches to the Use of Liquid Biopsy (Plasma ctDNA) Testing During Initial Diagnostic Workup in Eligible Patients With mNSCLC

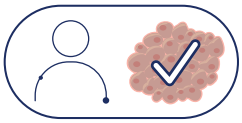
Patients **without tissue** sample for tumor testing

Plasma first approach: Perform liquid biopsy testing first in eligible patients with histologically confirmed mNSCLC. Note that liquid biopsy (plasma ctDNA) testing should not be done in lieu of a histologic tissue diagnosis. Perform rebiopsy for tumor tissue testing in case of a negative result.[22,52] 46% of patients who only received plasma testing had a clinically relevant mutation in one study[54]



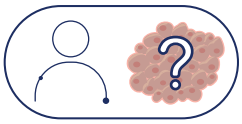
Patients with **adequate tumor** sample

Sequential approach: Test tumor tissue first. Perform liquid biopsy testing in case of incomplete genotyping.[22,52] In one study, the sequential approach increased identification of patients with actionable drivers by 65%[55]



Patients with tumor tissue of **questionable sufficiency**

Complementary approach: Perform liquid and tissue testing simultaneously. The complementary approach may reduce turnaround time and increase the yield of targetable alteration detection[22,52]



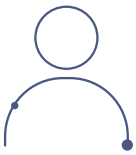
≈30% of samples may be false negative[23]

NCCN recommends that negative plasma ctDNA assay results should be confirmed by tumor tissue testing[22,52]

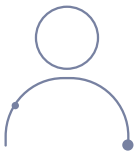
Intended to depict biomarker testing methodologies. When testing for therapy selection, please consult product prescribing information and FDA-approved companion diagnostics.

USE OF LIQUID BIOPSY

Incorporating liquid biopsies into testing algorithms may increase identification of patients with mNSCLC with actionable drivers[52,54,56-58]



13%-19%*
more patients were identified when tissue testing was added to liquid testing



9%-43%*
more patients were identified when plasma testing was added to tissue testing

**Based on 4 studies: The first was a prospective study on 210 patients with aNSCLC enrolled in an IRB-approved plasma NGS genotyping protocol at Memorial Sloan Kettering Cancer Center (New York) and Northern Cancer Institute (Sydney, Australia) from October 21, 2016, to January 1, 2018. The second was a prospective study on 307 patients with mNSCLC undergoing physician discretion SOC tissue genotyping at 1 of 28 North American centers. The third was a prospective study on 186 patients with treatment-naïve aNSCLC who were tested using a well-validated NGS cfDNA panel and SOC tissue testing. The fourth was a prospective study on 323 patients with stage IV NSCLC who underwent routine clinical testing at diagnosis or at disease progression at the Hospital of the University of Pennsylvania from April 1, 2016, to January 2, 2018.*

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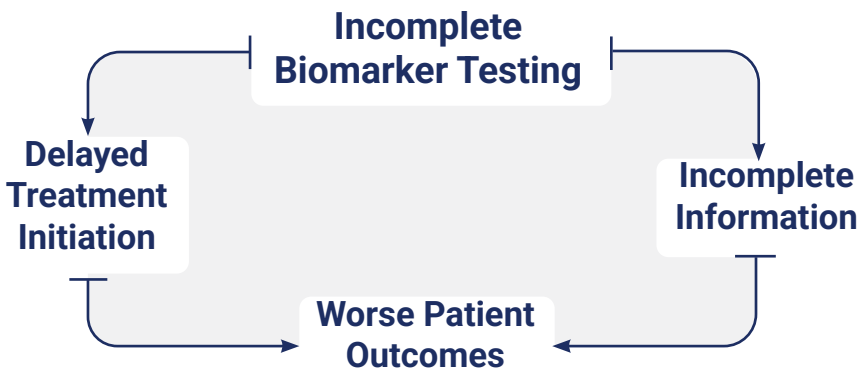
THE PERCEPTION OF BIOMARKER TESTING DOES NOT MATCH REALITY

	Perception[39]		Biomarker Testing Data From EHRs[59]	
Testing is ordered for actionable drivers	**97%**	of HCPs report testing for *EGFR*, *ALK*, *ROS1*, and *BRAF*	**<70%**	Less than 70% of patients were tested for *EGFR*, *ALK*, *ROS1*, *BRAF*, and PD-L1
Testing occurs prior to 1L	**95%**	of HCPs report testing before starting therapy	**<67%**	Fewer than 2/3 of patients had test results available before 1L treatment initiation
NGS is used most of the time	**93%**	of HCPs reported using NGS more than single-gene testing	**<33%**	Fewer than 1/3 of patients received NGS

Incomplete biomarker testing may lead to **delayed treatment initiation** if rebiopsy is needed or if treatment decisions are being made with **incomplete information,** both of which can be associated with **worse patient outcomes**[29,37,44,51,60,61]



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OPPORTUNITIES TO IMPROVE THE DIAGNOSTIC JOURNEY

Diagnostic hurdles

Obtaining sufficient tissue during biopsy

Inability to obtain a tissue biopsy

Tissue exhaustion

Long turnaround time

Potential for improvement

ROSE[46,47]	Allows assessment of tissue adequacy during biopsy	**Liquid biopsy**[52,53]	Minimally invasive procedure that provides tumor material for biomarker testing
NGS[24]	Allows simultaneous testing for multiple oncogenic drivers with less tissue than sequential gene testing for multiple biomarkers	**Reflex testing by pathologists**[24,51,62,63]	Eliminates waiting time for requesting physician to order molecular testing

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SUMMARY

NCCN, AMP, IASLC, and CAP agree: **Biomarker testing is recommended for eligible patients with mNSCLC**[22,23]

Biomarker testing depends on **MDT collaboration and communication**[25,64]

An independent retrospective analysis suggests patients with mNSCLC who received **care consistent with NCCN Guidelines had improved outcomes**[29]

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