Biomarker Testing in Advanced Lung Cancer

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Targeted Therapies for Advanced Lung Cancer Session
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Endorsed by
IASLC International Association for the Study of Lung Cancer
Conquering Thoracic Cancers Worldwide

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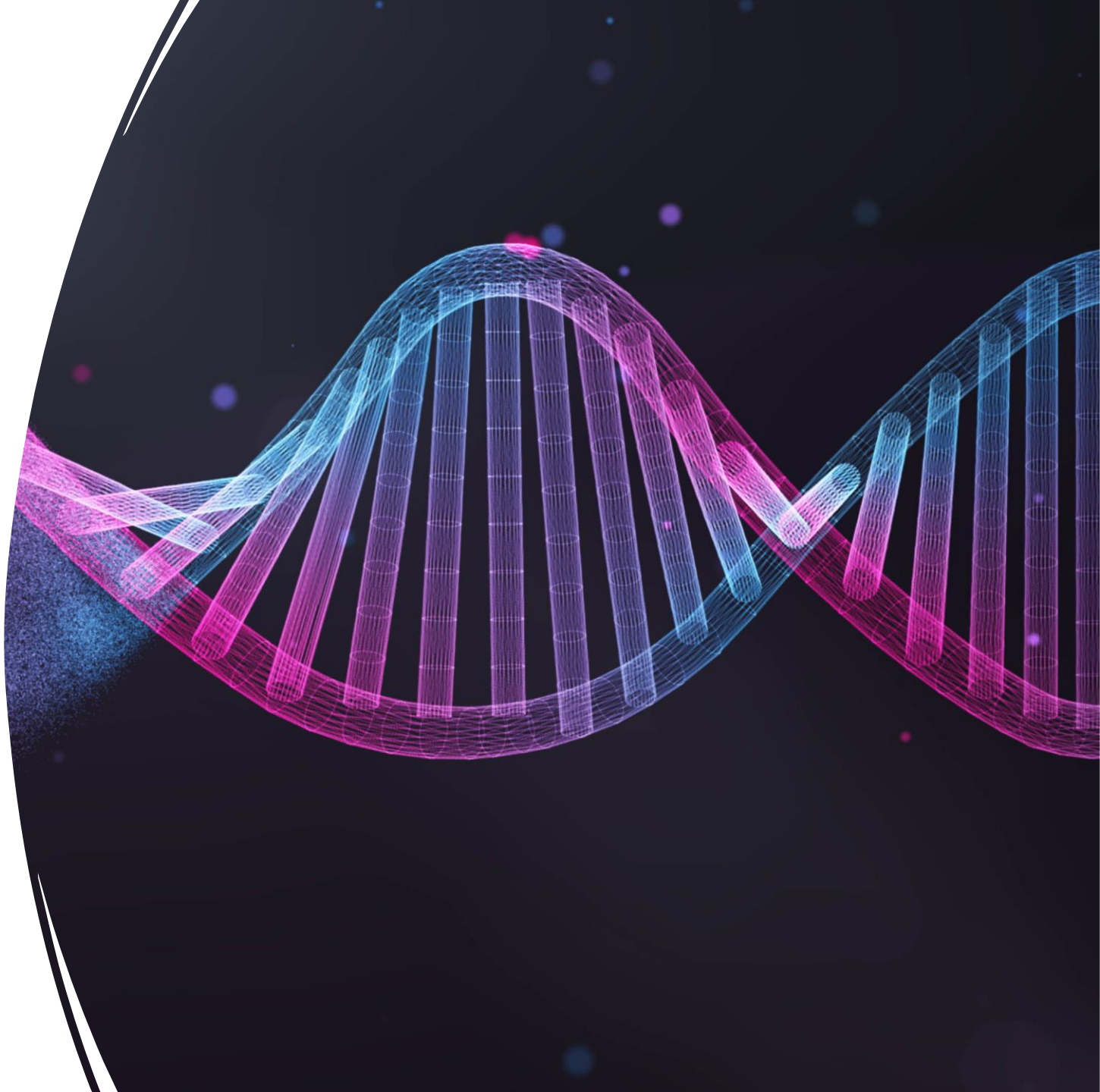
Biomarker Testing – Questions

1. What do we need to test for?
2. What patient populations needs to be tested?
3. When does testing need to be done?
4. How should the testing be done?
5. What is the optimal sequence for testing?

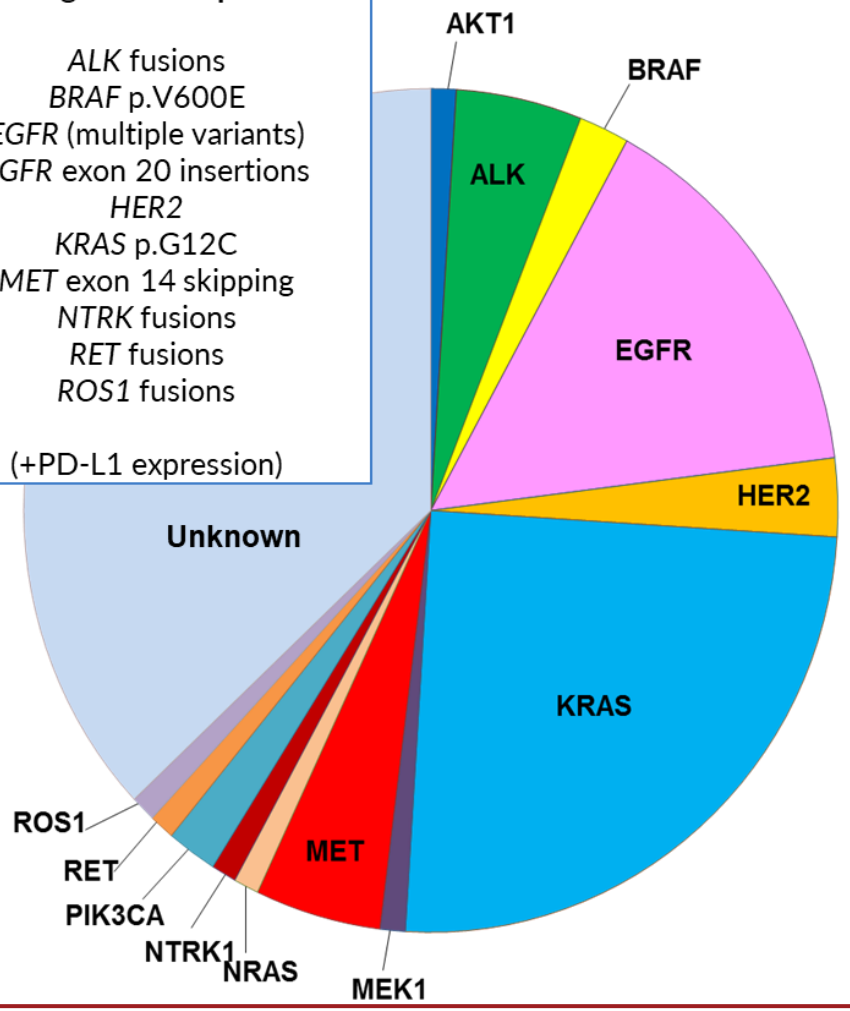


What do we need to test for?

10 targets with FDA-approved biomarker driven targeted therapies

ALK fusions
BRAF p.V600E
EGFR (multiple variants)
EGFR exon 20 insertions
HER2
KRAS p.G12C
MET exon 14 skipping
NTRK fusions
RET fusions
ROS1 fusions

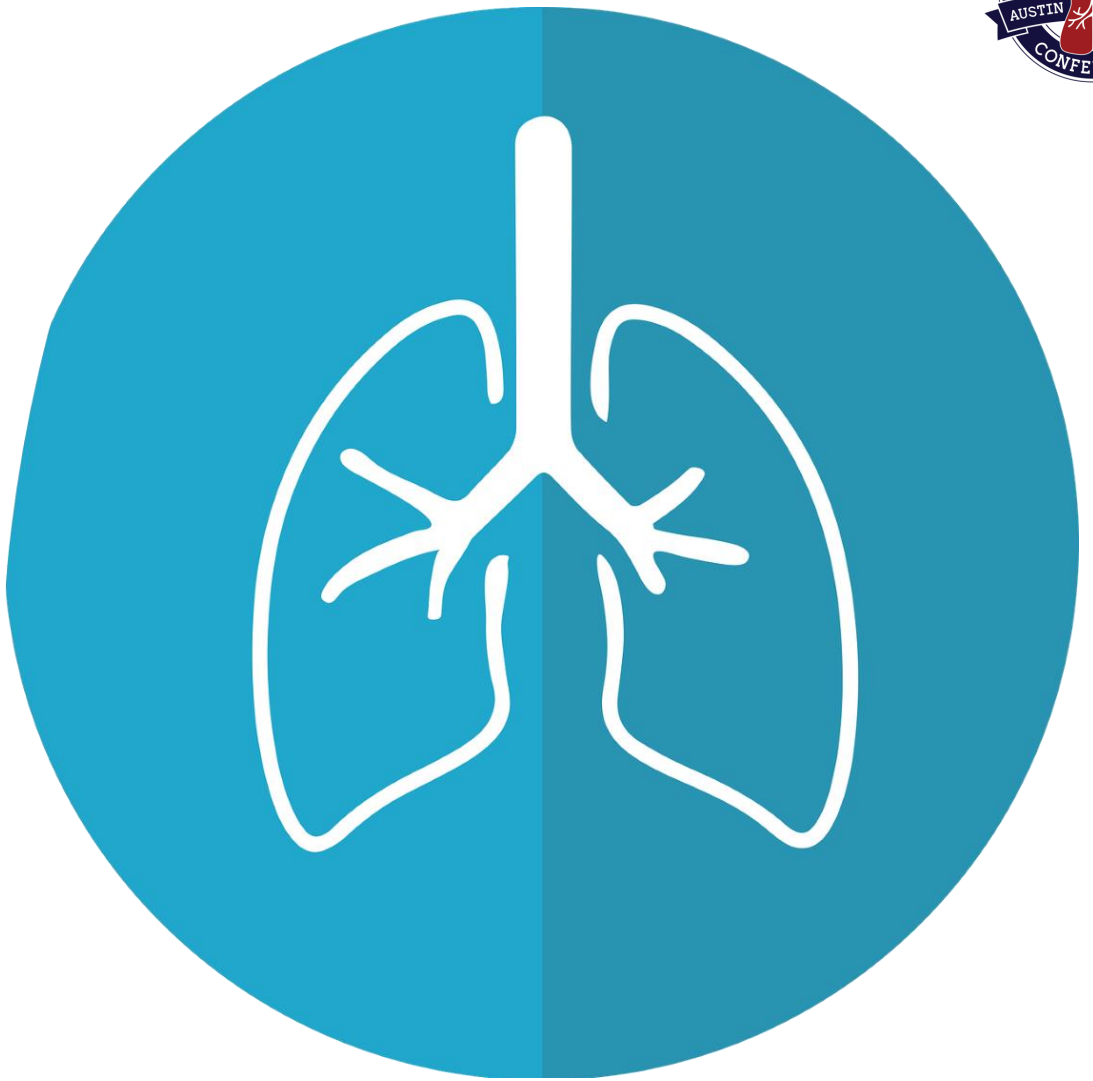
(+PD-L1 expression)



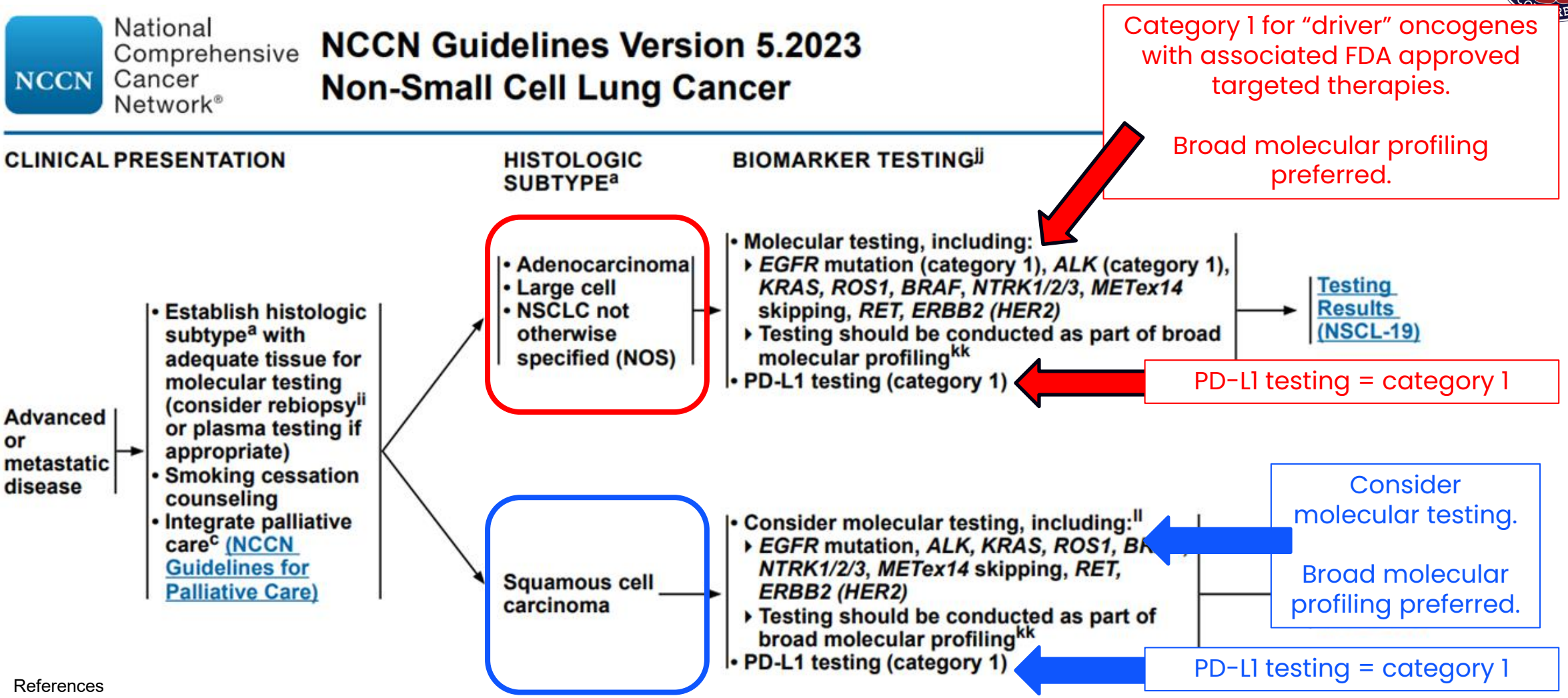
Target	Type of genomic alteration(s)	Example(s)	FDA approved Targeted Therapy
AKT1	SNVs	*AKT* E17K	
ALK	Fusions SNVs CNAs	*EML4-ALK* E13;A20 *ALK* L1196M *ALK* amplification	Yes
BRAF	SNVs Fusions	*BRAF* G469S/V/A, V600E, K601E, others *AGK-BRAF*	Yes
EGFR	SNVs Insertions/Deletions CNAs Fusions	*EGFR* L858R *EGFR* L747-A750>P *EGFR* amplification *EGFR-RAD51*	Yes
ErbB2 (HER2)	SNVs Insertions/Deletions CNAs	*ErbB2* V659E *ErbB2* exon 20 insertion *ErbB2* amplification	Yes
KRAS	SNVs	*KRAS* G12C, G12D, G13C, Q61H, others	Yes (for G12C)
MEK1	SNVs	*MEK1* K57N	
MET	SNVs Insertions/Deletions CNAs Fusions	*MET* D1228V *MET* exon 14 skipping alterations *MET* amplification *KIF5B-MET*	Yes
NRAS	SNVs	*NRAS* G12C, G12D, G13C, Q61H, others	
NTRK1	Fusions SNVs	*SQSTM1-NTRK1* *NTRK1* F589L	Yes
PIK3ca	SNVs	*PIK3ca* E545K	
RET	Fusions SNVs	*CCDC6-RET* *RET* G810C	Yes
ROS1	Fusions SNVs	*CD74-ROS1* *ROS1* G2032R	Yes

What patient populations need to be tested?

- Biomarker testing is incorporated into national and international guidelines for diagnosis and treatment of lung cancer.



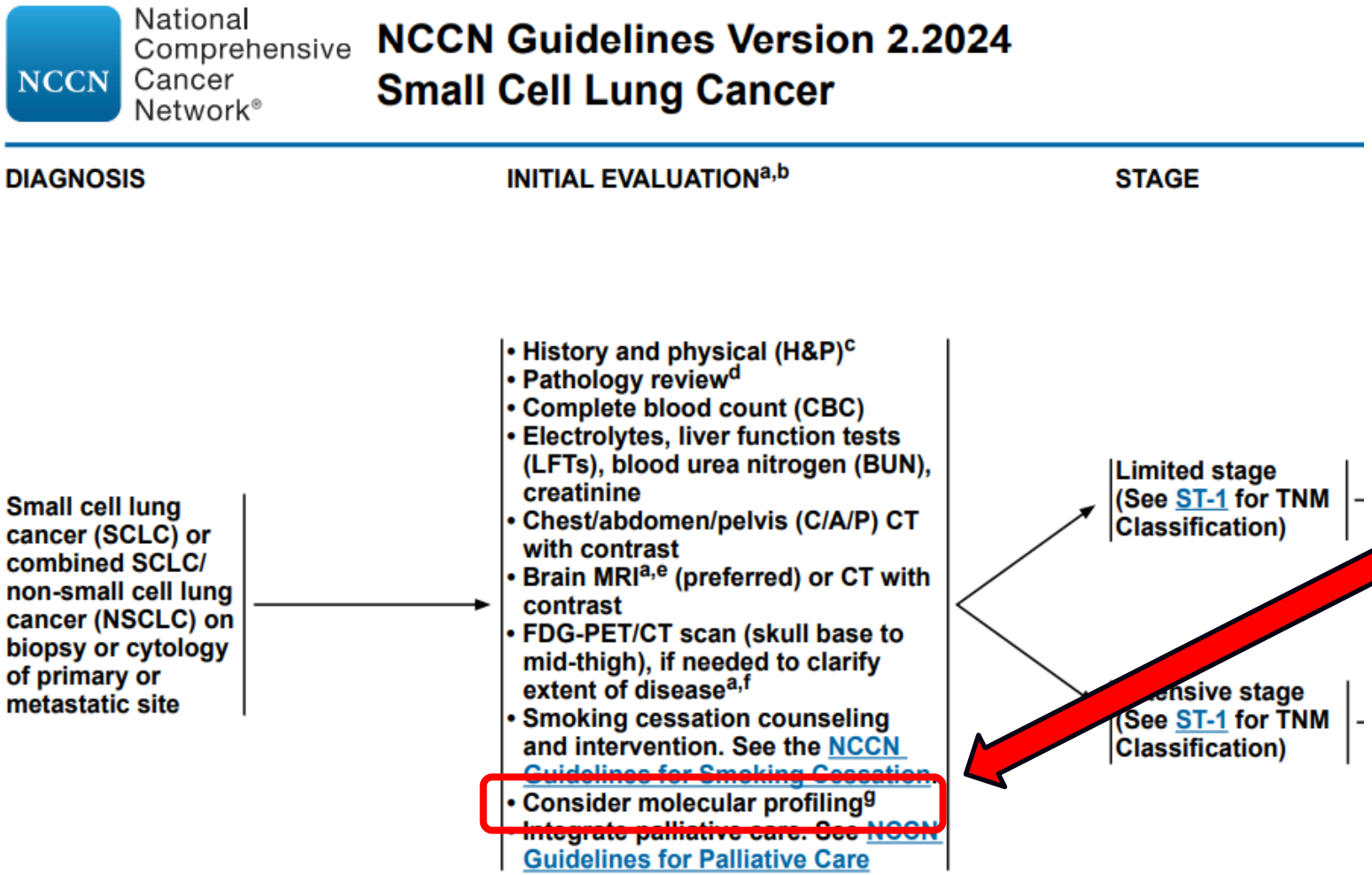
Non-Small Cell Lung Cancer



References

- NCCN NSCLC guidelines (Version 5.2023 — November 8, 2023) call out biomarker testing for stage IV (M1a and M1b) disease.

Small Cell Lung Cancer



"Comprehensive molecular profiling can be considered in rare cases—particularly for patients with extensive-stage/relapsed SCLC who do not smoke tobacco, lightly smoke, have remote smoking history, or have diagnostic or therapeutic dilemma, or at time of relapse—if not previously done, because this may change management."

How about patients with early-stage disease?

Adjuvant Therapy

EGFR mutations

Osimertinib FDA-approved for patients whose tumors harbor *EGFR* ex19del or L858R mutations, stages IB–IIIA, IIIB [T3,N2], based on ADAURA trial (Tsuboi NEJM July 2023)

PD-L1

Atezolizumab: FDA-approved for patients with resected stage IIB–IIIA, stage IIIB (T3, N2) with PD-L1 ≥1% and negative for EGFR ex19del or L858R mutations or ALK who received previous adjuvant chemotherapy (IMpower010, Felip Lancet 2021)

Pembrolizumab: FDA-approved for patients with resected stage IIB–IIIA, stage IIIB (T3, N2), or high-risk stage IIA NSCLC and negative for EGFR ex19del and L858R or ALK rearrangements who received previous adjuvant chemotherapy. "The benefit for patients with PD-L1 <1% is unclear." (KEYNOTE-091, Lancet Oncol 2022).

(ALK)

ALK rearrangements are exclusionary to PD-L1 directed therapies in the adjuvant setting. Emerging data (ALINA trial, ESMO 2023) on use of adjuvant ALK TKI, alectinib.

Neo-adjuvant Therapy

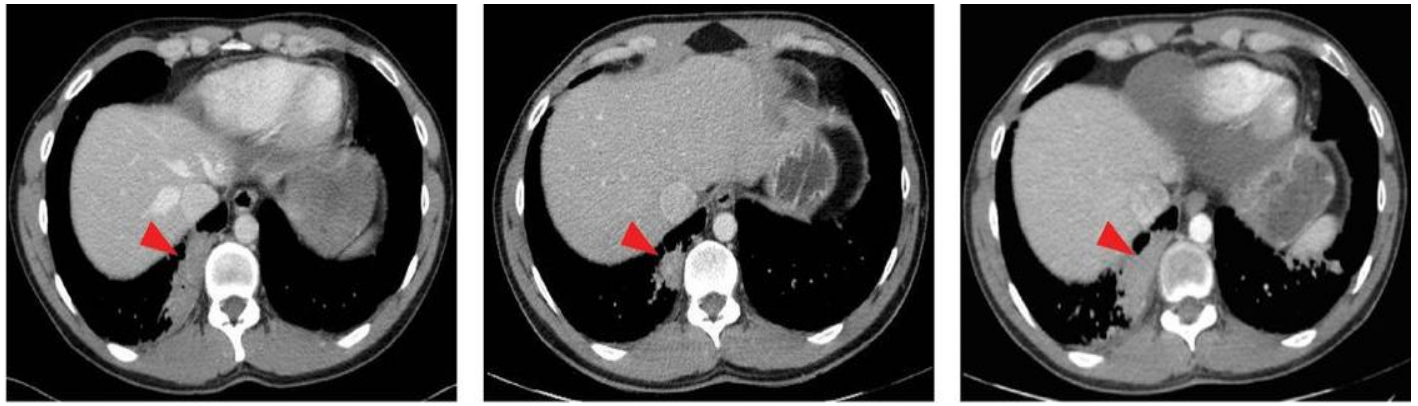
- A rapidly evolving topic!
- NCCN guidelines recommend "Test for PD-L1 status, EGFR mutations, and ALK rearrangements (stages IB–IIIA, IIIB [T3,N2])."
- Operational challenges.

When does testing need to be done?

➢ *Current standard of care*

- Patient with stage 4 *EGFR*-mutant lung cancer

Patient's treatment journey



Pre-targeted therapy (baseline)

Post 3 cycles (~3 months) of targeted therapy

Post 18 cycles (~18 months) of targeted therapy

- Before initiating therapy.
- To guide treatment selection.
- To guide enrollment into clinical trials.

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- To guide enrollment into clinical trials.

Future: Testing for surveillance /monitoring

How should the testing be done?

- *This is a huge topic.*

Table 1. Molecular methods for biomarker testing in solid tumors

Technique	Application	Advantages	Limitations
Immunohistochemistry (IHC)	protein-based assay for detection of expression	• cheap, rapid, and widely available • direct visualization of protein expression	• antibody availability • subjective interpretation/ quantification
Fluorescence *in situ* hybridization (FISH)	hybridization using fluorescent-labeled probes to detect gene copy-number changes or gene rearrangements/fusions	• relatively simple assay design • direct visualization of signals within cells of interest	• probe availability • restricted to specific locus/gene tested
Polymerase chain reaction (PCR)	detection of targeted gene mutations, fusions, copy-number alterations, DNA methylation	• high sensitivity and specificity • relatively simple assay design • relatively low-cost	• limited throughput • restricted to targeted genes and regions of interest interrogated
Next-generation sequencing (NGS)	massively parallel sequencing of multiple genes for detecting mutations, fusions, copy-number alterations	• high throughput • high sensitivity and specificity • comprehensive coverage • site/tumor-specific applications	• high complexity • bioinformatics requirements • longer turnaround time
Gene expression profiling (GEP)	differential gene expression between tumor/normal or pre/post-treated tumor	• high throughput	• bioinformatics requirements • restricted to targeted genes

Reference: Passaro A Cell Vol 187 Issue 7 28 March 2024

How should the testing be done?

➢ *This is a huge topic.*

Parameters of the test

- # of genes tested
  - Small panel
  - Large panel
  - Whole exome
- Type of sequencing
  - PCR vs. NGS
- Extent of sequencing of an individual gene
  - Hot spot vs. full exon
- DNA sequencing, RNA sequencing, both?
  - Some fusions may be better detected by ZNA

The analyte tested

- Tissue
  - typically from FFPE blocks
  - Core biopsy preferred over FNA
- Plasma (ctDNA)
- Both?

Practical concerns

- Turn around time
- Sample requirement
- Insurance coverage
- Local availability of a test

Excellent reference: 2023 IASLC ATLAS of MOLECULAR TESTING for TARGETED THERAPY in LUNG CANCER, available as a free download from the IASLC website: https://www.iaslc.org/research-education/publications-resources-guidelines/iaslc-atlas-molecular-testing-targeting

Some examples of currently available NGS panels
(there are *many* more!)

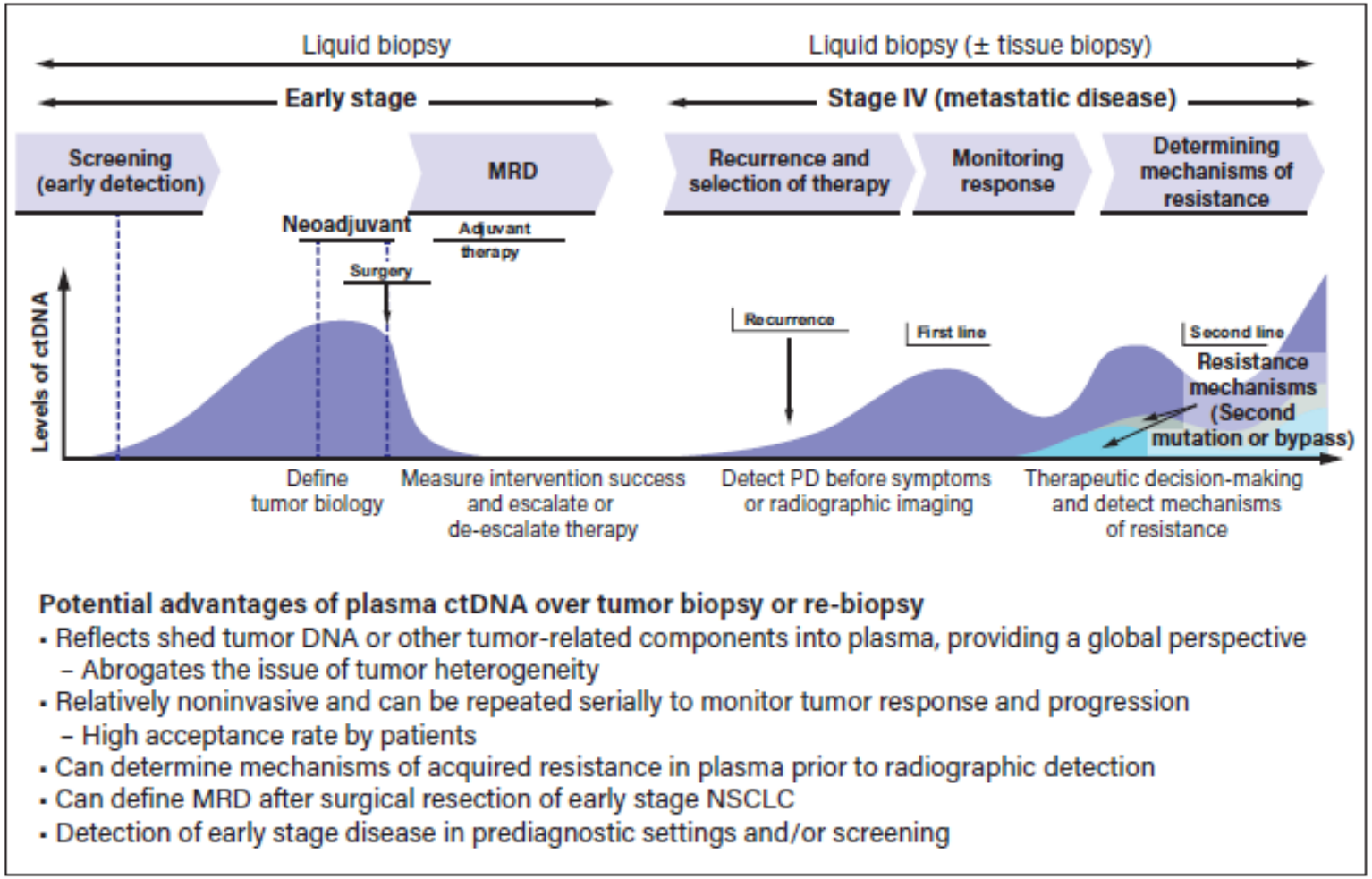
Table 5-2. Examples of Currently Available NGS Panel Tests

Biopsy type	Tissue biopsy					Liquid biopsy			
Source	DNA		RNA	Both		DNA			
Panel name	FoundationOne CDx (Foundation Medicine)	TruSight Tumor 26 assay (Illumina)	Archer FusionPlex Lung (Invitae)	Oncomine Dx Target Test (ThermoFisher Scientific)	TruSight Oncology Comprehensive (Illumina)	FoundationOne Liquid (Foundation Medicine)	Archer LiquidPlex (Invitae)	Guardant 360 (Guardant Health)	PlasmaSELECT (Personal Genome Diagnostics)
Material read	Tumor DNA	Tumor DNA	Tumor RNA	Tumor DNA or RNA	Tumor DNA or RNA	Circulating tumor DNA	Circulating free DNA	Circulating free DNA	Circulating tumor DNA
Enrichment	Hybrid capture	Amplicon	Hybrid capture	Amplicon	Hybrid capture	Hybrid capture	Hybrid capture	Hybrid capture	Hybrid capture
Sample required	FFPE tissue; 50-1000 ng DNA	FFPE tissue; 30-300 ng	FFPE tissue; 10 ng RNA	FFPE tissue; 10 ng DNA, 10 ng RNA	FFPE tissue; ≥20 mm^3 or 40 ng DNA and 40 ng RNA	2 × 8.5 mL blood samples	5-10 ng DNA	10 mL blood sample for 5-30 ng DNA	2 × 10 mL blood samples
Number of genes	324 genes and 36 fusions	26 genes	17 genes and 16 fusions	23 genes and 21 fusions	523 genes and 55 fusions	70 genes	28 genes	73 genes	64 genes
Turnaround time	<2 weeks	2-3 days	2 days	3 days	~1 week	<2 weeks	2-3 days	7 days	Not reported

Abbreviations: FFPE = formalin-fixed paraffin-embedded; NGS = next-generation sequencing.

Source: IASLC ATLAS OF MOLECULAR TESTING FOR TARGETED THERAPY IN LUNG CANCER, 2023

Liquid Biopsy across the cancer care continuum



Potential advantages of plasma ctDNA over tumor biopsy or re-biopsy

- Reflects shed tumor DNA or other tumor-related components into plasma, providing a global perspective
  - Abrogates the issue of tumor heterogeneity
- Relatively noninvasive and can be repeated serially to monitor tumor response and progression
  - High acceptance rate by patients
- Can determine mechanisms of acquired resistance in plasma prior to radiographic detection
- Can define MRD after surgical resection of early stage NSCLC
- Detection of early stage disease in prediagnostic settings and/or screening

Source: IASLC ATLAS OF MOLECULAR TESTING FOR TARGETED THERAPY IN LUNG CANCER, 2023

Beyond genotyping: where are we going with liquid biopsy in patients with advanced / metastatic NSCLC?

- What is the best type of ctDNA assay to use to assess clearance?
- What is the optimal limit of detection to call "MRD" in the advanced disease setting?

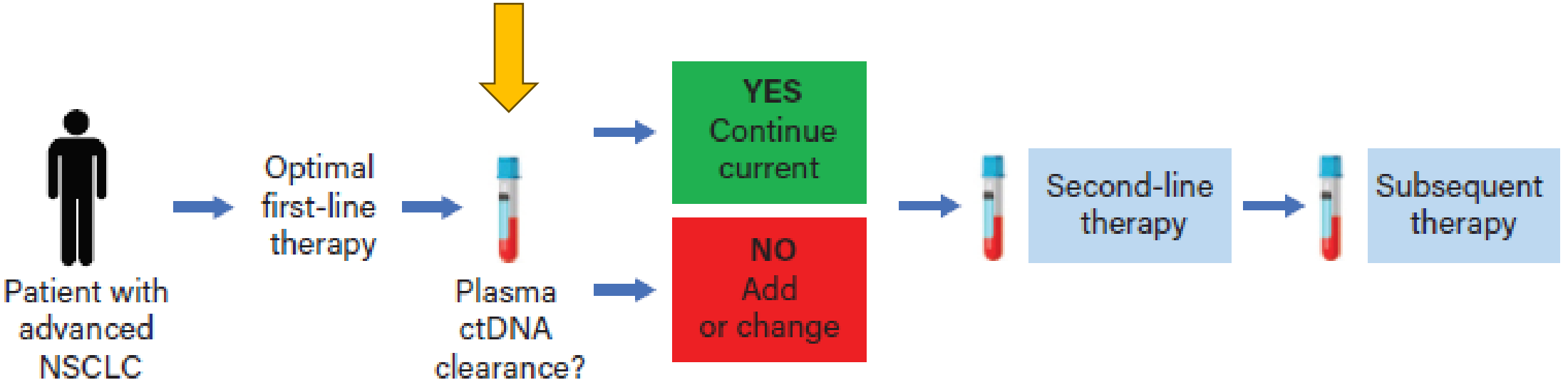


Figure 4-7. Future integration of liquid biopsy monitoring into treatment decision-making. Abbreviations: ctDNA = circulating tumor DNA; NSCLC = non-small cell lung carcinoma.

Source: IASLC ATLAS OF MOLECULAR TESTING FOR TARGETED THERAPY IN LUNG CANCER, 2023

What is the optimal sequence for testing?

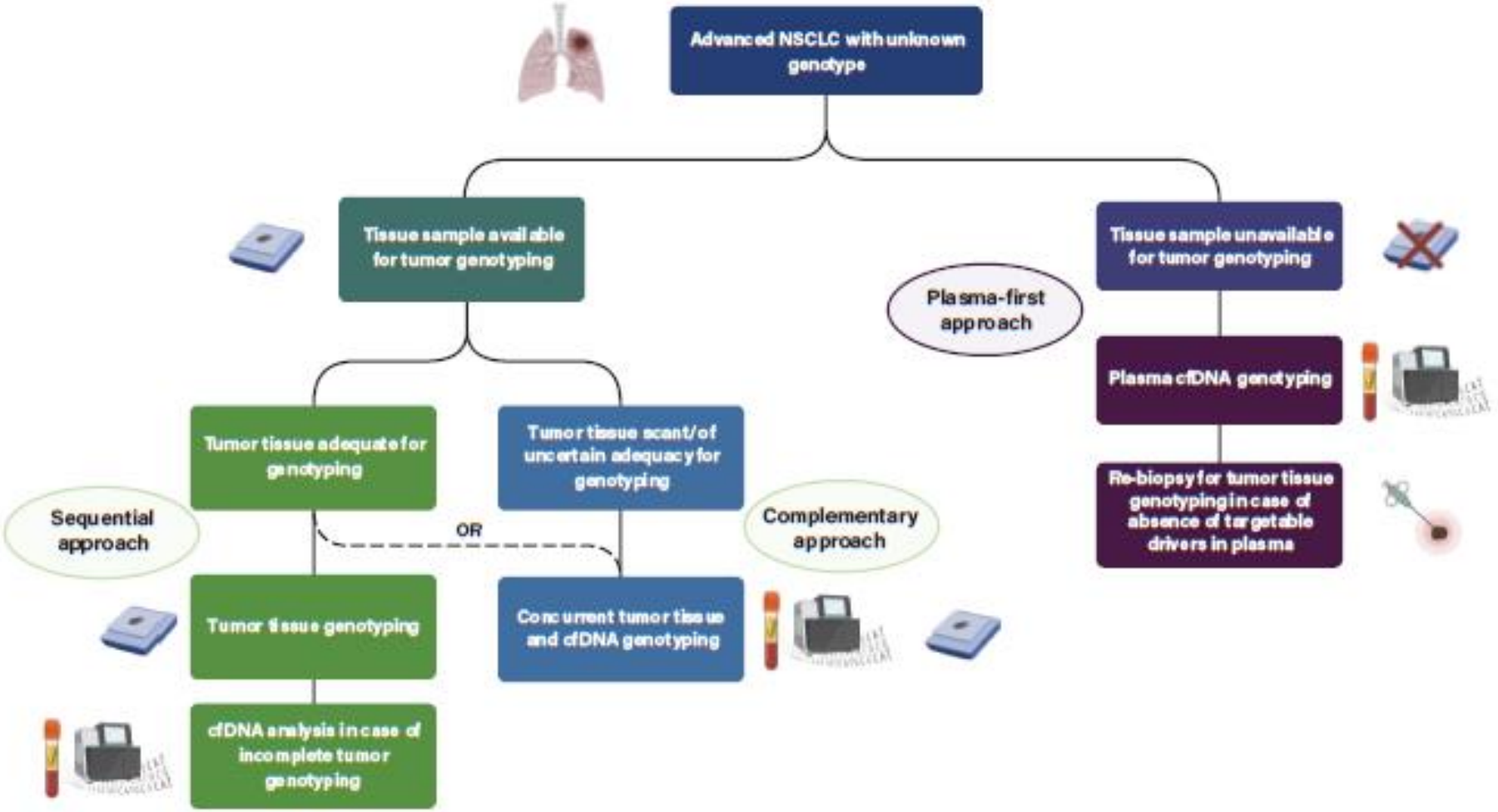


Figure 4-4. Diagnostic algorithm for liquid biopsy use in treatment-naïve advanced non-small cell lung cancer (NSCLC) (Adapted from Rolfo et al.[16])

Source: IASLC ATLAS OF MOLECULAR TESTING FOR TARGETED THERAPY IN LUNG CANCER, 2023

A Challenging Case

- 72yo female never smoker diagnosed with cT2aN2M1a lung adenocarcinoma.
- Diagnostic biopsy sent for PD-L1 and tissue NGS by the pulmonologist ('reflex testing')
  - PD-L1 = 75%
  - Tissue NGS = tumor quantity not sufficient (with testing company #1) that uses a large panel (~400 gene) assay
- Patient seen in medical oncology → what are the next steps to get molecular / biomarker testing results? Options:
  1) Send liquid biopsy
  2) Order repeat tissue biopsy
  3) Both
- Plan:
  - Liquid biopsy ordered in clinic on the day of the consultation.
  - Repeat tissue biopsy ordered; scheduled in 3 weeks.

A Challenging Case: 72yo F never smoker

- 3 weeks past; patient has her 2nd tumor biopsy.
  - A requests for extra cores was made prior to the biopsy procedure, in order to maximize tumor material yield for required biomarker testing. 5 total cores obtained.
  - Pathologist review: tumor "borderline" quantity for NGS (with company #2)
- What now?

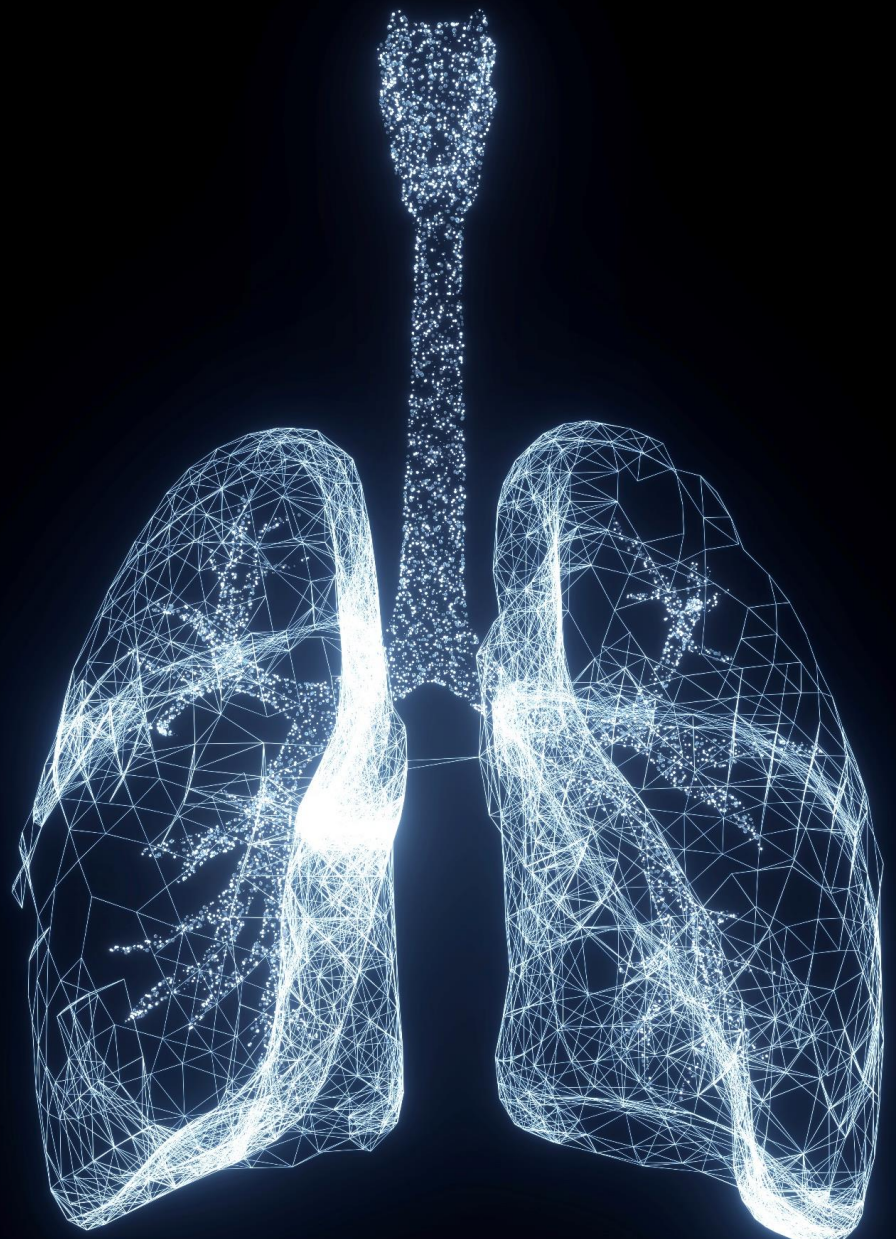
Options

1. The liquid biopsy result is enough to rule out actionable alterations. Start systemic therapy.
2. Order a third biopsy to attempt to get tissue NGS again before starting systemic therapy.
3. Send available material from the second biopsy for a smaller panel sequencing, requiring less input material, focusing on the biomarkers with FDA approved indications only.
4. Send a liquid biopsy to a different company (for example, a company with more data supporting fusion detection in the blood).

A Challenging Case: 72yo F never smoker

The outcome of this case

- Through discussions with pathology and the testing companies, the second biopsy was sent for smaller panel testing and FISH for fusions → still quantity not sufficient.
- Through discussions with the proceduralists, the patient did undergo a third biopsy with even more keen focus on intra-procedural assessment of tumor quantity.
- The third biopsy was (barely) sufficient for tumor tissue NGS.
  - In discussions with the MSL for the testing company, the testing was able to be 'expedited'.
- The patient's tumor harbored a ROS1 fusion → started on TKI.



Closing Questions / Topics for Discussion

- Should all biomarker testing for lung cancer be reflexed? Who “owns” that order?
- How can we move away from (cumbersome) PDF documents of NGS reports that are ancillary to a patient’s medical record?
- How can NGS reports be harmonized and streamlined to improved readability by providers?
- How will we move beyond single biomarker → single drug to multiple biomarkers (simple example: KRAS/STK11, EGFR/TP53)?
- How do we best train and educate our lung cancer work force?
- How we do operationalize complex genomically based precision medicine for lung cancer patients with equity?

Thank you for the invite to your beautiful city!

I would be happy to discuss in more detail anytime!

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