LIQUID BIOPSY TO IDENTIFY ACTIONABLE BIOMARKERS IN mNSCLC

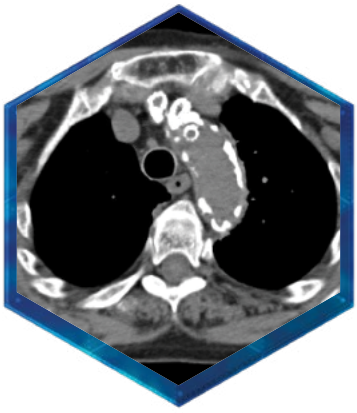
60-year-old female patient[a]

Patient Information:

- **Background:** Teacher who enjoys spending time with her grandchildren
- **Past Medical History:** Bronchitis, glaucoma, mild hypertension
- **Smoking History:** 1 pack per day for 4 years, 30 years ago
- **History of Present Illness:** Presents with cough, pain in the chest, and weight loss

Evaluation:

- **ECOG PS:** 0
- **CT Scan:** Bilateral lung lesions
- **Tissue Biopsy:** CT-guided CNB; suspicious for advanced lung cancer
  - Sufficient tissue for 10 sections/slides
  - Needs: 1 slide for H&E, 1 slide for TTF-1 IHC, and 8 slides to send out for NGS and PD-L1 IHC



Scan provided by Joeffrey Chahine

Preliminary Diagnosis: Stage IV adenocarcinoma of the lung

How would you identify actionable biomarkers for this patient and avoid rebiopsy?

Diagnostic testing for mutations can identify patients more likely to benefit from a targeted therapy[1,2]

- However, **~20%** of patients have inadequate tumor tissue for molecular analysis at diagnosis[3,4]
- Repeat biopsies are not feasible in almost **20%** of patients with advanced NSCLC[4]
- Almost **25%** of repeat biopsies fail to yield sufficient material for genomic analysis[4]

Liquid biopsy is a diagnostic technique that measures either cell-free DNA (cfDNA), circulating tumor cells (CTCs), or tumor exosomes from bodily fluids such as blood, urine, or saliva[5,6]

cfDNA
Detects mutations from small fragments of tumor DNA released into the bloodstream

CTC
Correlates disease activity with number of cells released from the primary tumor mass into the bloodstream

Tumor Exosomes
Extracts molecular information from actively released vesicles derived from tumor cells

Blood-based NGS has the potential to overcome some of the limitations associated with tissue collection and testing, which may enable clinicians to offer personalized therapies[7]

	NGS on Liquid Biopsy[7-10]	NGS on Tissue Biopsy[7,11]
Invasiveness	Peripheral blood draw	Invasive procedure
Efficiency	Quick and easily performed	Biopsy is time-intensive
Evidence for treatment selection	Less evidence for treatment selection	Substantial evidence for treatment selection
Sample requirement (per lab guidance)	10-20 mL blood	≥8 slides

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60-year-old female patient[a] (continued)

Biomarker Testing Results:

Genomic alteration identified by NGS on liquid biopsy but no genomic alteration detected by NGS on tissue biopsy (quantity not sufficient/test not performed/preanalytic factors)

How would you interpret these biomarker results?

IASLC

From an IASLC statement paper[12]: *"A positive finding of an actionable mutation in ctDNA, if using a validated assay represents sufficient evidence to initiate targeted treatment."*

A prospective study of 323 patients with metastatic NSCLC who had blood-based biomarker testing ordered as part of routine clinical management showed that[13]:

44% of eligible patients were unable to get complete genomic results from tissue biopsy

~2× as many patients had targeted alterations detected by liquid biopsy and tissue testing (n=82) vs tissue testing alone (n=47)

A global phase II/III, multicohort study to evaluate the relationship between blood-based biomarkers and the clinical activity of targeted therapies or immunotherapy, in patients with treatment-naïve advanced/metastatic NSCLC presented at ESMO[14]:

5.4% (n=119/2219) prevalence of *ALK* rearrangements in the screening population was close to the expected rate of 5%

Liquid biopsy may be used to test for important biomarkers in NSCLC, including *ALK*, *BRAF*, *EGFR*, *MET*, *RET*, and *ROS1*[8-10]

- CLIA-certified labs may offer blood-based cfDNA NGS tests validated to detect the guidelines-recommended biomarkers in advanced NSCLC[9,10]
- **NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)** recommend repeat biopsy and/or plasma testing if there is insufficient tissue to allow testing for all of *EGFR, ALK, ROS1, BRAF, MET,* and *RET*; plasma testing can be considered if the patient is medically unfit for invasive tissue sampling[15]
- An **IASLC statement paper** notes that liquid biopsy can be considered at the time of initial diagnosis in all patients who need tumor molecular profiling, but it is particularly recommended when tumor tissue is scarce, unavailable, or a significant delay potentially greater than 2 weeks is expected in obtaining tumor tissue[12]

[a]Hypothetical patient case.

ALK = anaplastic lymphoma kinase; BRAF = B-Raf proto-oncogene; cfDNA = cell-free deoxyribonucleic acid; CLIA = Clinical Laboratory Improvement Amendments; CNB = core needle biopsy; CT = computerized tomography; CTC = circulating tumor cell; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; ESMO = European Society for Medical Oncology; H&E = hemolin and eosin; IASLC = International Association for the Study of Lung Cancer; IHC = immunohistochemistry; MET = MET proto-oncogene; mNSCLC = metastatic non–small cell lung cancer; NCCN = National Comprehensive Cancer Network; NGS = next-generation sequencing; NSCLC = non–small cell lung cancer; PCR = polymerase chain reaction; PD-L1 = programmed death-ligand 1; PS = performance status; RET = RET proto-oncogene; ROS1 = ROS proto-oncogene 1; TTF-1 = thyroid transcription factor-1.

References:

1. Tsao MS, Hirsch FR, Yatabe Y. IASLC Atlas of ALK and ROS1 Testing in Lung Cancer. 2016. **2.** Lindeman NI, et al. *J Molec Diagn.* 2018;20:129-159. **3.** Lim C, et al. *Ann Oncol.* 2015;26:1415-1421. **4.** Chouaid C, et al. *Lung Cancer.* 2014;86:170-173. **5.** Gold B, et al. *J Mol Diagn.* 2015;17:209-224. **6.** Diaz LA, et al. *J Clin Oncol.* 2014;32:579-586. **7.** Merker JD, et al. *J Clin Oncol.* 2018;36:1631-1641. **8.** FoundationOne Medicine. https://www.foundationmedicine.com/test/foundationone-liquid. Accessed July 16, 2020. **9.** Guardant Health. https://guardanthealth.com/. Accessed June 23, 2020. **10.** NeoGenomics. https://neogenomics.com/sites/default/files/2020-04/Liquid_Biopsy_ProductSheet_042320_Final.pdf. Accessed June 23, 2020. **11.** Hovelson DH, et al. *Neoplasia.* 2015;17:385-399. **12.** Rolfo C, et al. *J Thorac Oncol.* 2018;13:1248-1268. **13.** Aggarwal C, et al. *JAMA Oncol.* 2019;5:173-180. **14.** Gadgeel SM, et al. Presented at ESMO 2019 Congress. Abstract 5026. **15.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.6.2020. © National Comprehensive Cancer Network, Inc 2020. All rights reserved. Accessed June 22, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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