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Best Practices When Choosing Tissue or Liquid Biopsy Specimens For Biomarker Testing in Non-Small Cell Lung Cancer (NSCLC)

Judy S. Wang, MD - Associate Director of Drug Development Unit, Florida Cancer Specialists & Research Institute

John Fox, MD, MHA – Senior Medical Director, Illumina

June 17, 2025

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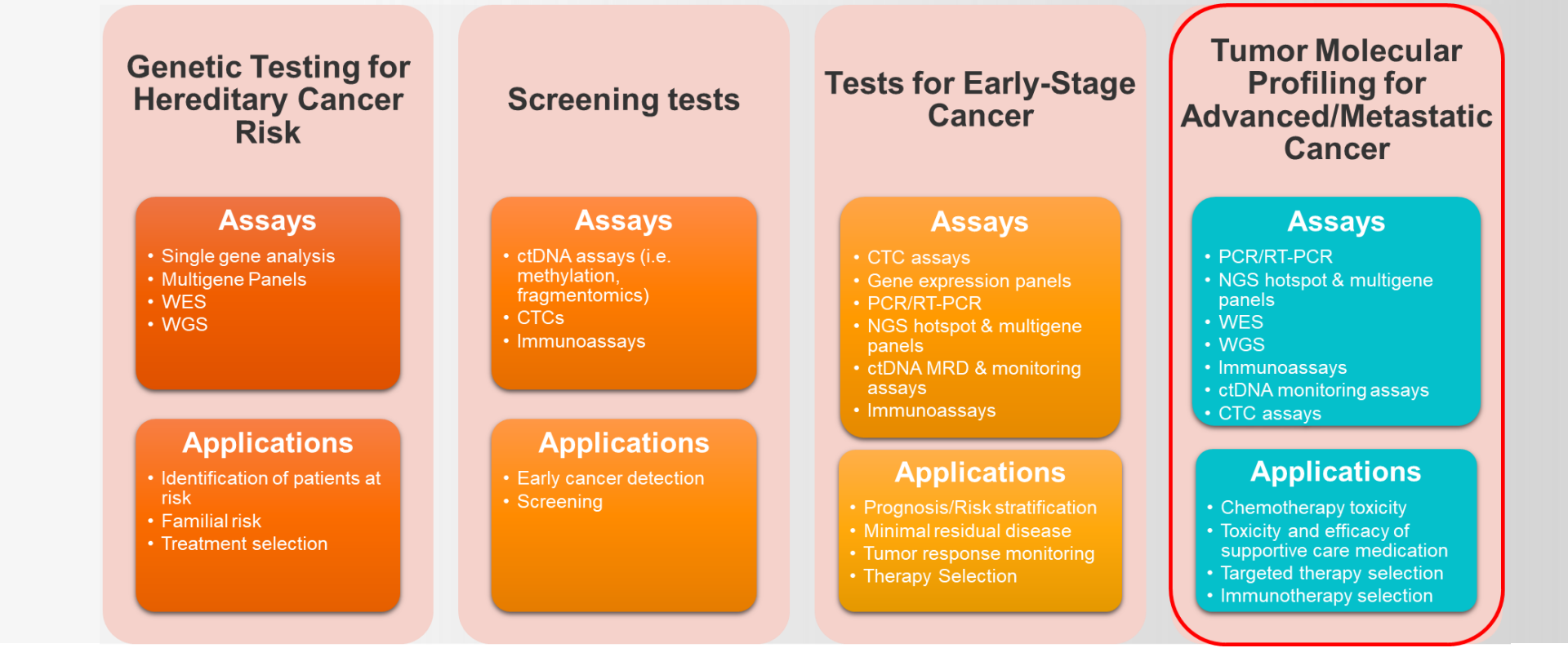
Biomarker testing for NSCLC: Background

Molecular Diagnostics in Clinical Oncology



WES=whole-exome sequencing; WGS=whole-genome sequencing; CTCs= circulating tumor cells; ctDNA=circulating tumor DNA; PCR=polymerase chain reaction; RT-PCR=reverse transcription polymerase chain reaction; NGS=next generation sequencing; MRD=minimal residual disease

Adapted from Sokolenko AP, Imyanitov EN.Front Mol Biosci. 2018 Aug 27;5:76

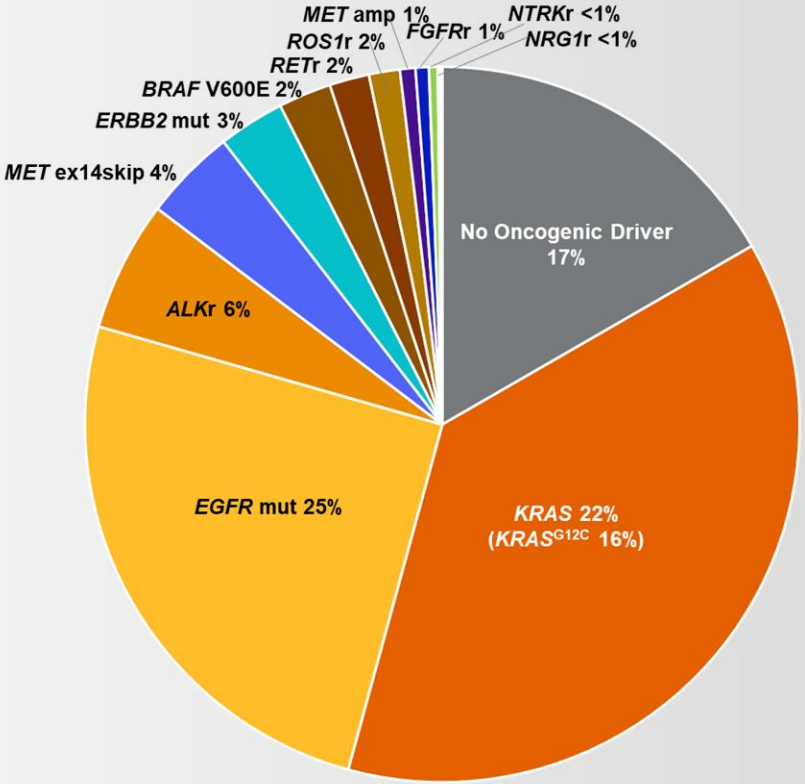
>50% of Advanced NSCLC Patients Harbor an Actionable Oncogenic Driver Alteration

ALK
Crizotinib
Alectinib
Ceritinib
Lorlatinib
Brigatinib
Ensartinib

EGFR mut
Gefitinib
Erlotinib
Afatinib
Osimertinib
Dacomitinib
Amivantamab+lazertinib

KRAS^{G12C}
Sotorasib
Adagrasib

NTRK fusion
Entrectinib
Larotrectinib
Repotrectinib



EGFRex20ins
Amivantamab

METex14
Capmatinib
Tepotinib
Crizotinib

ERBB2 (HER2)
Trastuzumab deruxtecan
Trastuzumab emtansine

ROS1 fusion
Crizotinib
Entrectinib
Repotrectinib
Ceritinib

BRAF V600E
Dabrafenib+trametinib
Encorafenib+binimetinib

RET fusion
Selpercatinib
Pralsetinib
Cabozantinib

NSCLC=non-small cell lung cancer; amp=amplification; mut=mutation; r=rearrangement

Adapted from Odintsov I, Sholl LM. Pathology. 2024;56(2):192-204.
National Cancer Institute. (n.d.). Targeted therapy drug list. National Institutes of Health. https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/approved-drug-list#targeted-therapy-approved-for-lung-cancer

Real-World Biomarker Testing Rates and Turnaround Times Within a Large Community-Based Oncology Network

Retrospective observational chart review of patients with metastatic NSCLC (n=3474)

90% pts had testing for at least one biomarker, and **<50% received all 5 biomarker tests***

TAT from test order to results was ~2 weeks. Median time from diagnosis to 1L treatment was ~5 weeks

Only 35% had test results for **all 5 biomarkers** before 1L treatment

NGS testing rates increased with time, but **remained below 50%** over the study period

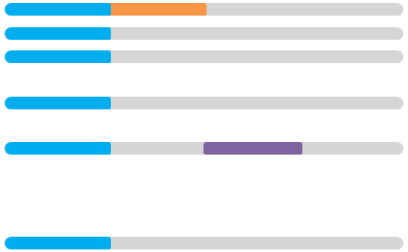
**EGFR, ALK, ROS1, BRAF,* and PD-L1 were assessed*
NSCLC=non-small cell lung cancer; TAT=turnaround time; 1L=first-line; pts=patients; NGS=next-generation sequencing
Robert NJ, Espirito JL, Chen L, et al. Lung Cancer. 2022 Apr;166:197-204

Comprehensive Genomic Profiling (CGP) can Identify More Clinically Relevant Variants than Conventional Testing Approaches

Single Marker Testing

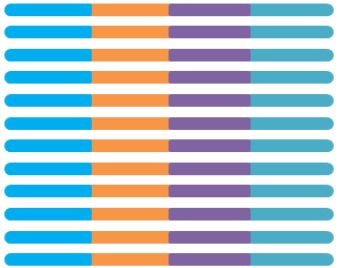
- Identifies mutations in a single gene using conventional approaches like FISH, PCR, or IHC[1]
- Would miss clinically relevant mutations in other genes[2,3]

Hotspot Panel



- Interrogates specific mutations in select genes[4,5]
- Would miss other clinically relevant classes of alterations and mutations in other genes[2,4-7]

Comprehensive Genomic Profiling



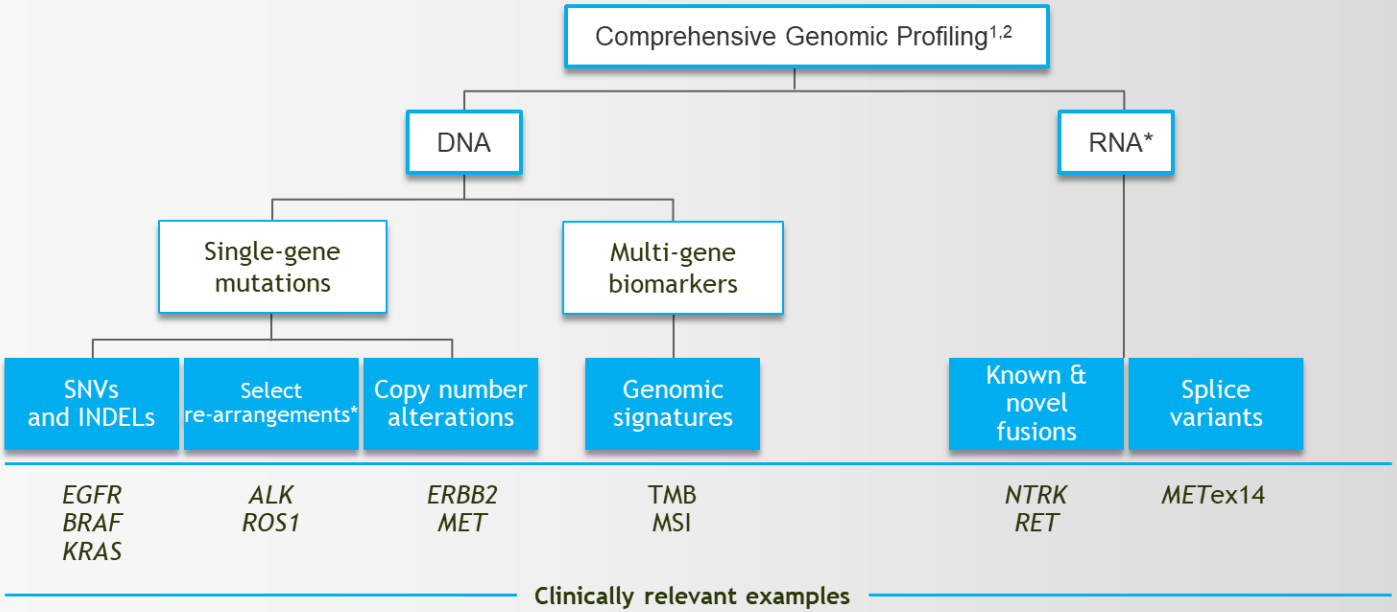
Analyzes all four types of genomic mutations across a large panel of cancer-related genes and genomic signatures (ie, TMB, MSI)[8,9]

Base substitutions | Insertions and deletions | Rearrangements | Copy number alterations | No genomic alterations detected

CGP=comprehensive genomic profiling; FISH=fluorescence in situ hybridization; IHC=immunohistochemistry; MSI=microsatellite instability; PCR=polymerase chain reaction; TMB=tumor mutational burden

1. Malone ER, Oliva M, Sabatini PJB, Stockley TL Siu LL. Genome Med. 2020;12:8; 2. Reitsma M, Fox J, Borre PV, et al. J Manag Care Spec Pharm. 2019;25(5):601-611; 3. Ali SM, Hensing T, Schrock AB, et al. *Oncologist*. 2016;21:762-770; 4. Singh RR, Patel KP, Routbort MJ, et al. J Mol Diagn. 2013;15(5):607-622; 5. Kopetz S, Mills Shaw KR, Lee JJ, et al. JCO Precis Oncol. 2019;3:PO.18.00213; 6. Zehir A, Benayed R, Shah RH, et al. Nat Med. 2017;23(6):703-713; 7. Drilon A, Wang L, Arcila ME, et al. Clin Cancer Res. 2015;21(16):3631-3639; 8. Kroeze LI, de Voer RM, Kamping EJ, et al. J Mol Diagn. 2020;22(6):757-769; 9. Pestinger V, Smith M, Sillo T, et al. Mol Diagn Ther. 2020;24(3):339-349

Comprehensive Genomic Profiling (CGP) Facilitates Biomarker Testing



Advantages of CGP:

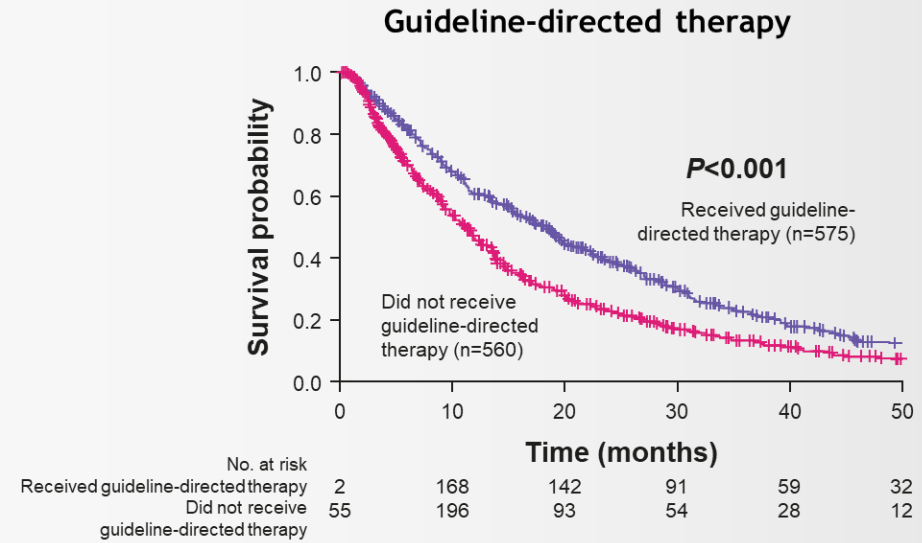
- ✓ Optimizes the yield of actionable findings[1,2]
- ✓ Enables tissue stewardship[3]
- ✓ Detects rare or infrequent variants, including fusions[2]
- ✓ Broad genomic coverage for accurate calling of genomic signatures[4]

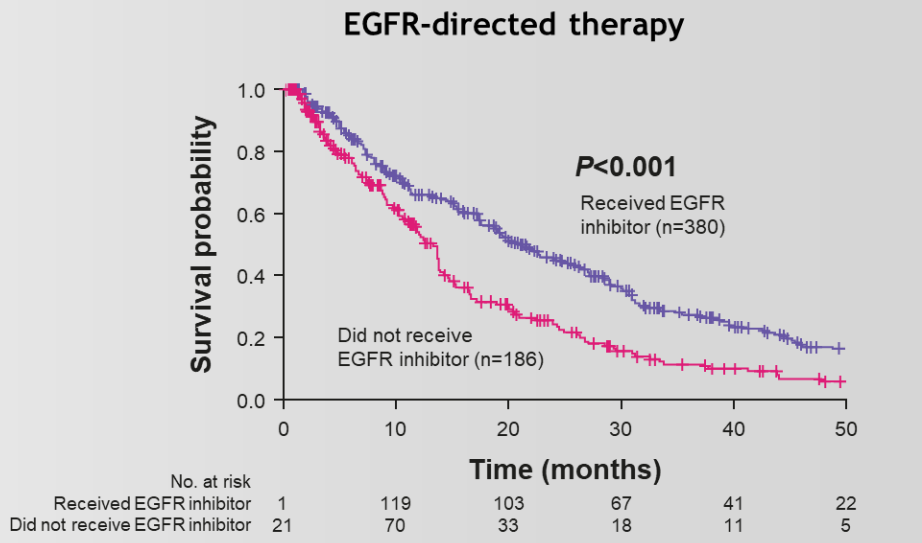
*Not all CGP assays bait for rearrangements in DNA and RNA

CGP=comprehensive genomic profiling; NGS=next-generation sequencing; INDELs=insertions and deletions; SNVs=single nucleotide variants; HRD=homologous recombination deficiency; TMB= tumor mutational burden; MSI=microsatellite instability

1. Kopetz S, Mills Shaw KR, Lee JJ, et al. JCO Precis Oncol. 2019;3:PO.18.00213; 2. Drilon A, Wang L, Arcila ME, et al. Clin Cancer Res. 2015;21(16):3631-3639; 3. Yu TM, Morrison C, Gold EJ, et al. Clin Lung Cancer. 2019 Jan;20(1):20-29.e8; 4. Chalmers ZR, Connelly CF, Fabrizio D, et al. Genome Med. 2017 Apr 19;9(1):34

Improved Survival in NSCLC Patients Receiving CGP with Genomically-Matched Targeted Therapies





CGP=comprehensive genomic profiling; EHR=electronic health record; NSCLC=non-small cell lung cancer

Singal G, Miller PG, Agarwala V, et al. JAMA. 2019;321(14):1391-1399

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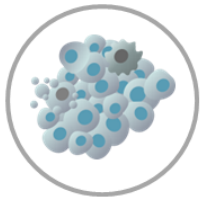
Choosing tissue and/or liquid biopsy specimens

Biomarker Testing for NSCLC

Benefits & Limitations When Using Tissue or Liquid Biopsies for Biomarker Testing

	Advantages	Limitations
Tumor tissue 	• Pathology information • PD-L1 assessment • **High sensitivity** • RNA for fusion detection	• Invasive • Represents snapshot of tumor genomics • Longer TAT • Rebiopsy not always feasible
Liquid biopsy 	• Less invasive, easy serial testing • **Captures intra- & intertumoral heterogeneity** • Rapid TAT	• ctDNA fraction depends on tumor shed rate • Lower sensitivity for detecting all alteration types when ctDNA fraction is low • Result interference by CHIP

ctDNA=circulating tumor DNA; CHIP=clonal hematopoiesis of indeterminate potential; PD-L1=programmed cell death ligand 1; TAT=turnaround time.

Rolfo C, Mack P, Scagliotti GV, et al. J Thorac. Oncol. 2021;16(10):1647-1662.

Opportunities for Precision Medicine are Missed Up to 30% of the Time Due To Tissue Insufficiency

Frequency of tissue insufficiency

NSCLC[1-2]

Tissue insufficiency due to *quantity or quality* is a barrier to NGS

Factors influencing QNS:

- Biopsy procedure[3]
- Tumor percentage[4]
- Tissue handling and fixation[5]
- Prior testing[6]

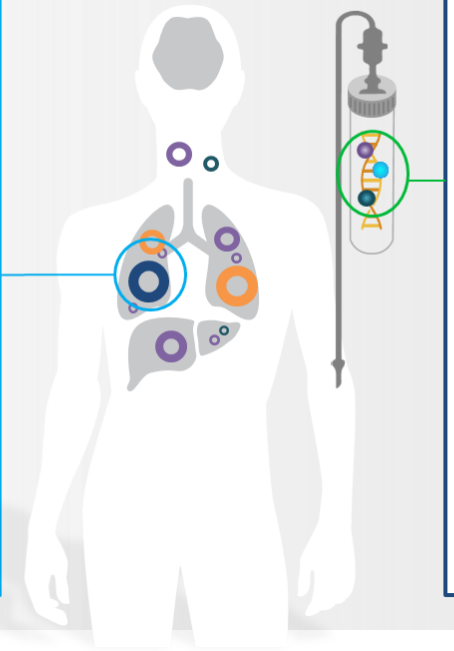
NGS=next-generation sequencing; NSCLC=non-small cell lung cancer; QNS=quantity not sufficient

1. Hagemann IS, Devarakonda S, Lockwood CM, et al. Cancer. 2015;121(4):631-639; 2. Aggarwal C, Thompson JC, Black TA, et al. JAMA Oncol. 2019;5(2):173-180; 3. Mata DA, Harries L, Williams EA, et al. Arch Pathol Lab Med. 2023;147(3):338-347; 4. Goswami RS, Luthra R, Singh RR, et al. Am J Clin Pathol. 2016;145(2):222-237; 5. Hussain M, Corcoran C, Sibilla C, et al. Clin Cancer Res. 2022;28(8):1518-1530; 6. Drilon A, Wang L, Arcila ME, et al. Clin Cancer Res. 2015;21(16):3631-3639

Factors Influencing ctDNA Levels and Detection

Disease characteristics

- Tumor type
- Tumor burden and staging
- Disease status (stable vs progressive disease)
- Tumor microenvironment (stroma and vascularization)



Other factors

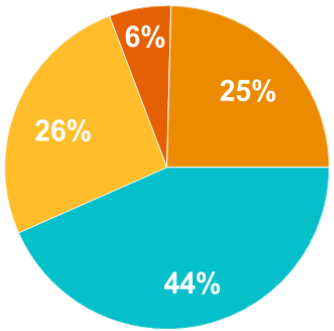
- Sample timing related to treatment or procedures
- Sample acquisition, transport, and processing procedures
- Type of variant
- Assay sensitivity

Not all patients may be candidates for liquid biopsy at a given time

ctDNA=circulating tumor DNA

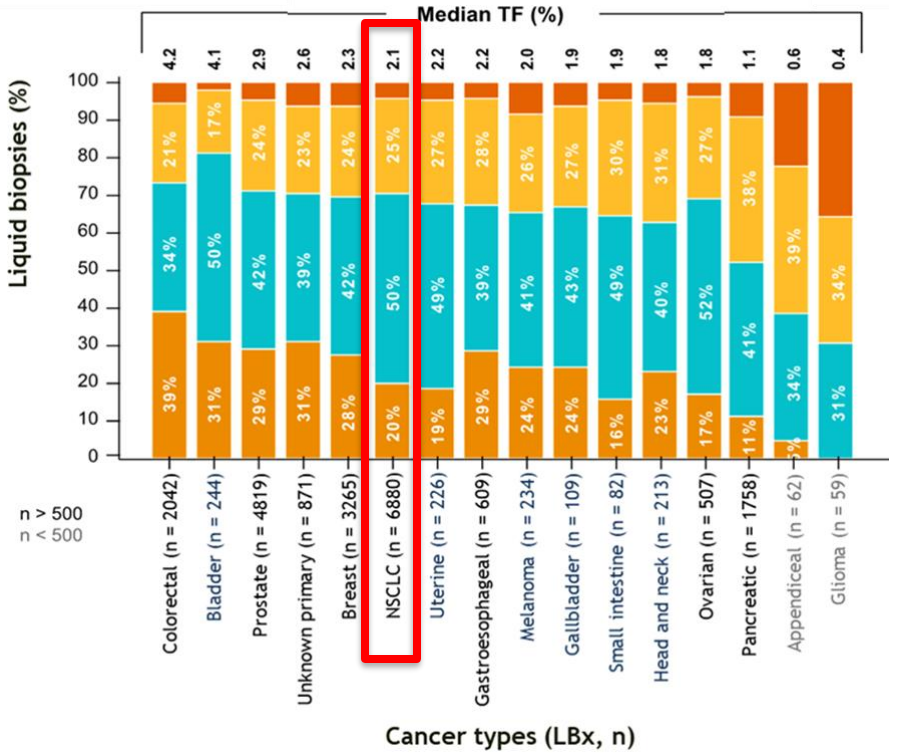
Vivancos A, Tabernero J. Nat Med. 2022;28(11):2255-2256

ctDNA Detection Rate Varies Across Tumor Types



Entire cohort (23,482)

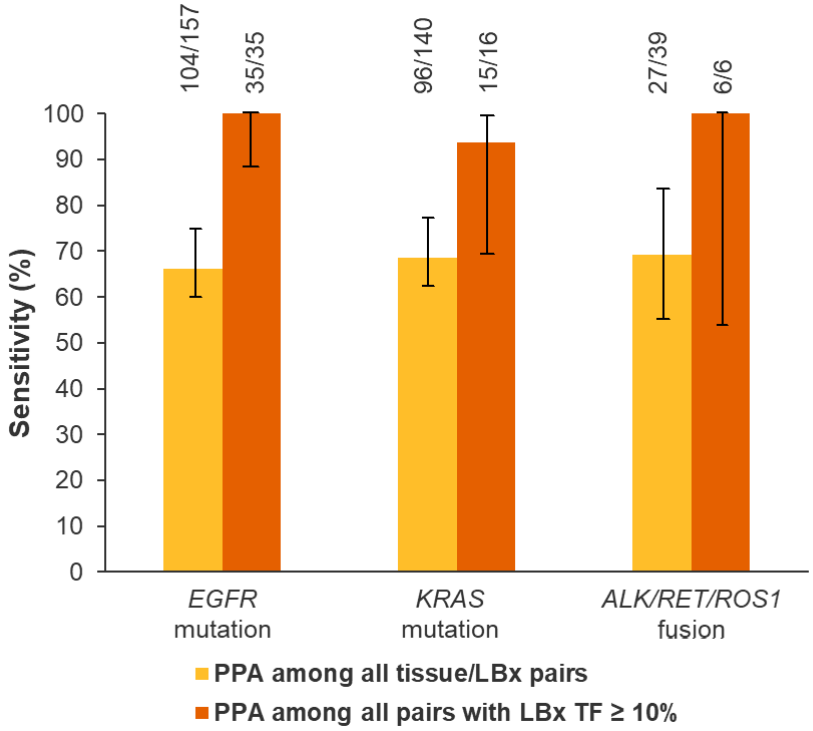
ctDNA fraction
- ≥ 10%
- (1%-10%)
- 0%-1%
- Not detected

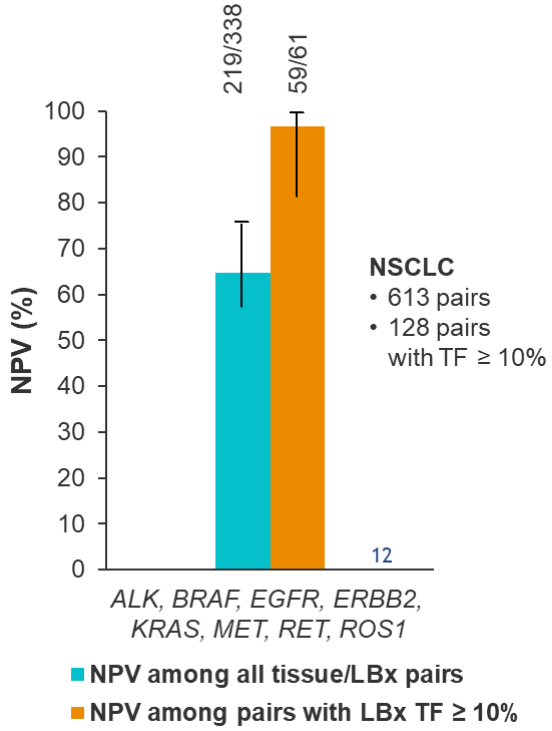


ctDNA=circulating tumor DNA; GIST=gastrointestinal stromal tumor; LBx=liquid biopsy; NSCLC=non-small cell lung cancer; SCLC=small cell lung cancer; TF=tumor fraction

Husain H, Pavlick DC, Fendler BJ, et al. JCO Precis Oncol. 2022;6:e2200261

Sensitivity and Specificity With Liquid Biopsies is Higher in Samples with High ctDNA Fraction



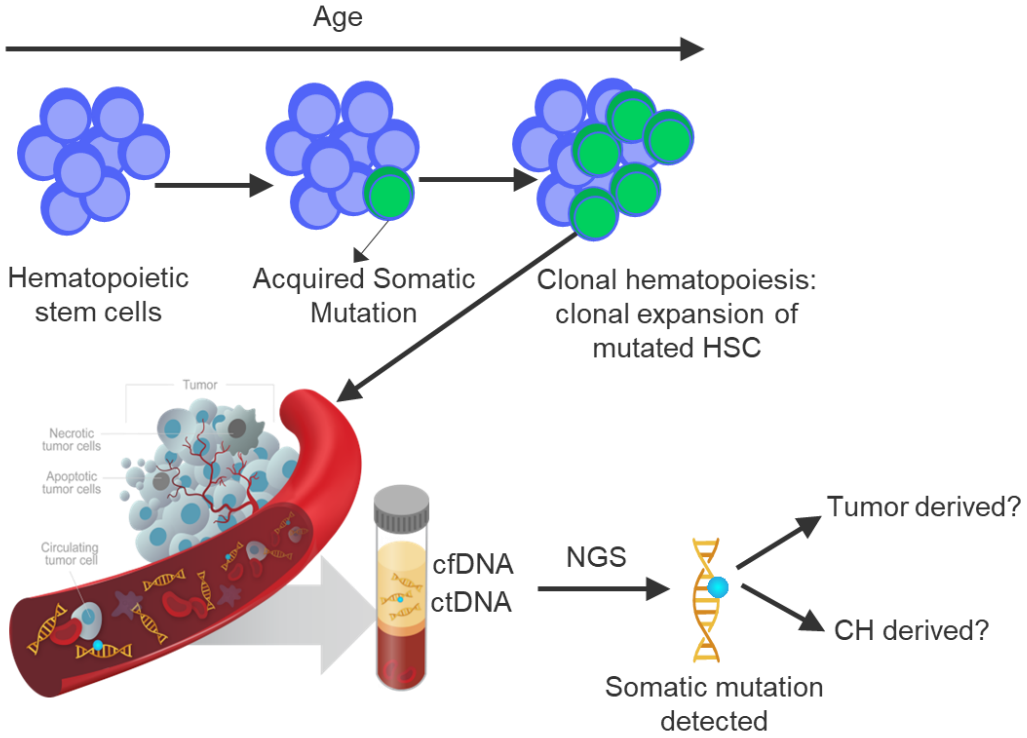


Reflexing to tissue may be considered to confirm negative findings if the TF is low

LBx=liquid biopsy; NPV=negative predictive value; PPA=percent positive agreement; TF=tumor fraction

Husain H, Pavlick DC, Fendler BJ, et al. JCO Precis Oncol. 2022;6:e2200261

Clonal Hematopoiesis Mutations Detected in Plasma From Liquid Biopsy Specimens Can Mimic Tumor-Derived Mutations



Clonal Hematopoiesis (CH)

- CH somatic mutations can occur in known oncogenes and are detected along with tumor-derived somatic mutations via NGS of liquid biopsy specimens
- Misclassification of CH mutations as tumor-derived (false-positive) may lead to inappropriate treatment decisions
- Cancer patients with CH are at risk of therapy-related myeloid neoplasms

1. Jaiswal S, Fontanillas P, Flannick J, et al. N Engl J Med. 2014;371(26):2488-2498; 2. Ptashkin RN, Mandelker DL, Coombs CC, et al. JAMA Oncol. 2018;4(11):1589-1593; 3. Chan ICC, Wiley BJ, Bolton KL. Front Oncol. 2022;12:794021 4. Köhnke T, Majeti R. Cancer Discov. 2021;11(12):2987-2997

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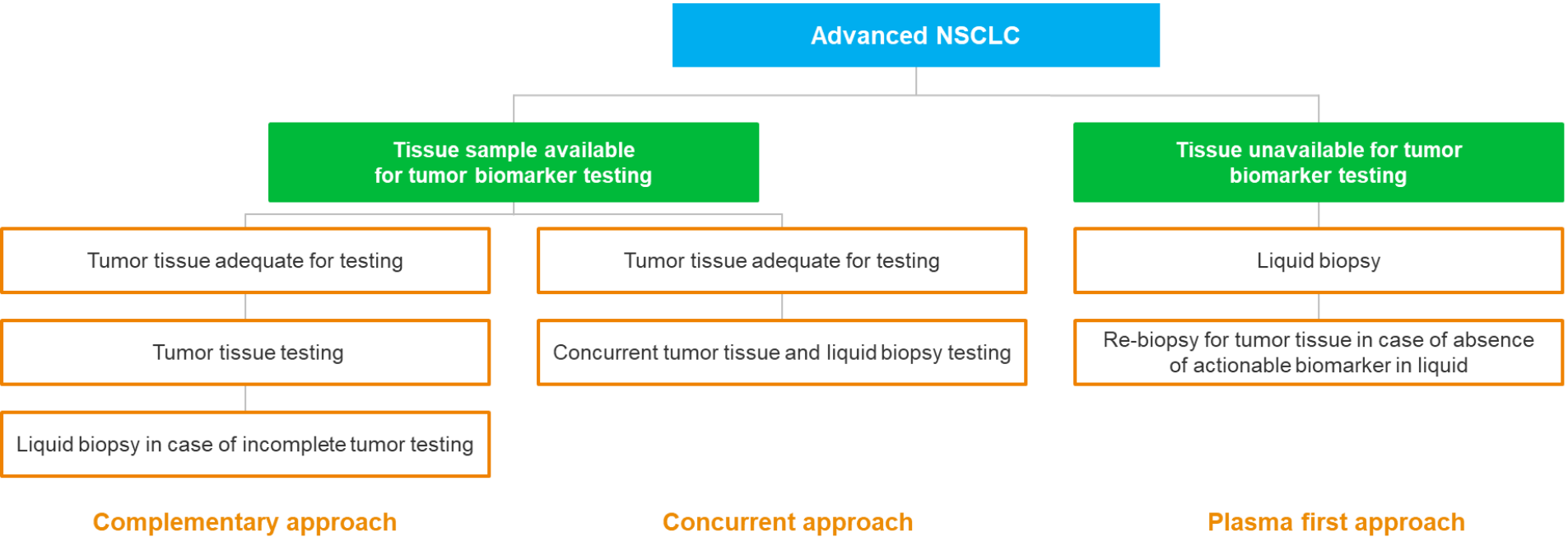
Clinical utility of tissue & liquid biopsy specimens

Biomarker Testing for NSCLC

Guidance for Oncologists: International Association for the Study of Lung Cancer (IASLC)



NSCLC=non-small cell lung cancer

Rolfo C, Mack P, Scagliotti GV, et al. J Thorac Oncol. 2021 Oct;16(10):1647-1662

Compromised Outcomes in Patients with NSCLC Treated Prior to the Report of an Actionable Oncogenic Driver (AOD) Alteration

Group A

(Comparator group)
379 pts **treated after report of AOD**

Group B

47 pts **started treatment before report of AOD and switched to TKI** within 35 days

Group C

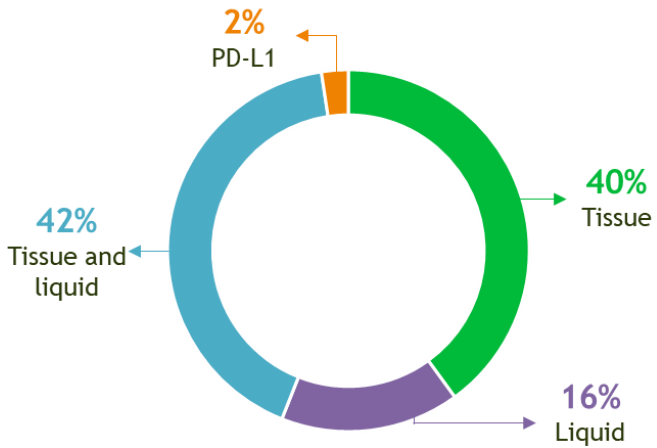
84 pts **started treatment before report of AOD and not switched to TKI** within 35 days

	Group A (N=379)	Group B (N=47)	Group C (N=84)
OS			
Median (95% CI, months)	**28.8 (23.3,34.6)**	**21.7 (12.2,NR)**	**15.3 (11.5,19.7)**
Hazard ratio	Reference	1.12	1.62
P-Value	-	0.59	0.003
Time to next treatment			
Median (95% CI, months)	**13 (10.5,15.5)**	**5.5 (3.4,8.9)**	**6.4 (4.9,8.7)**
Hazard ratio	Reference	1.73	1.71
P-Value	-	0.002	0.0002

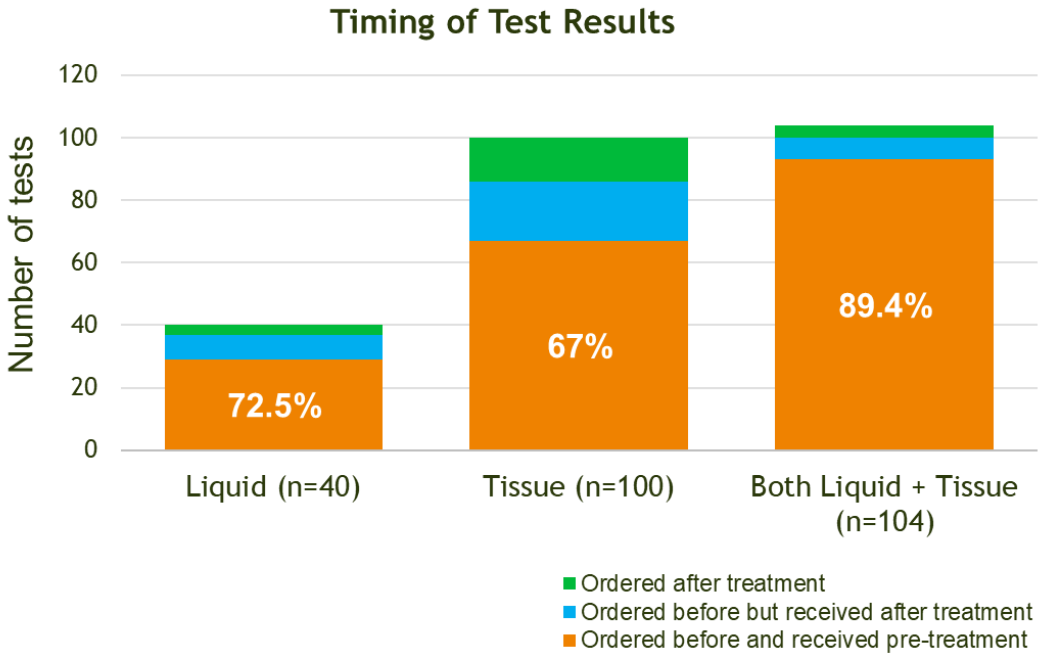
Outcomes are significantly compromised in patients harboring AOD but who are treated initially or even in patients quickly switched to TKI

Time to next treatment: day1 line of treatment 1 to day 1 line of treatment 2 or apparent death; in group B is determined after the switch to TKI.
NSCLC=non-small cell lung cancer; AOD=actionable oncogenic driver; TKI=tyrosine kinase inhibitor; OS=overall survival; CI=confidence interval
Scott J.A., Lennerz J., Johnson M.L., et al. JCO Oncol Pract. 2023 Aug 9;OP2200611

Real-World Tissue and Liquid Biopsy Utilization in Advanced NSCLC in a Large Community US Practice



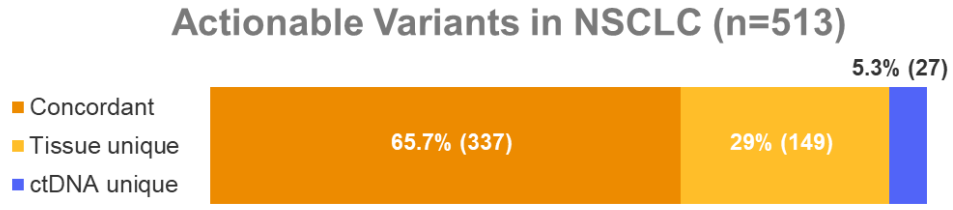
TAT (days)	Average	Median
Tissue (n=204)	16.7	11
Liquid (n=144)	7.9	7

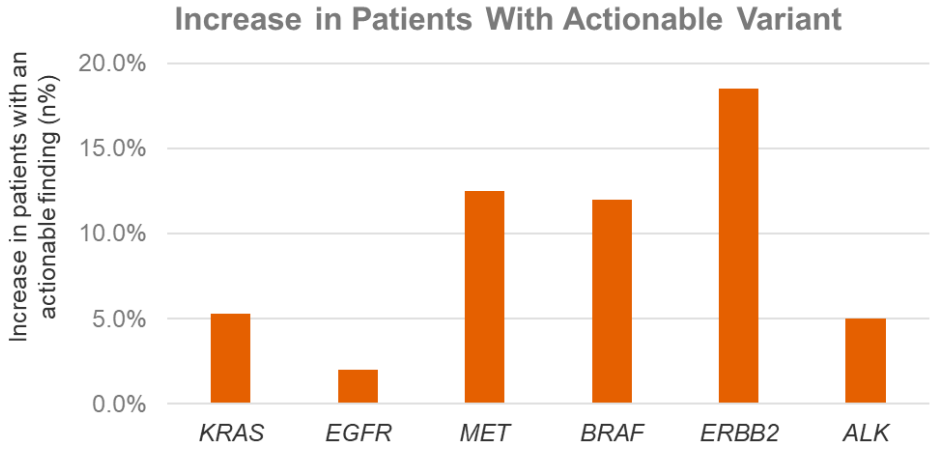


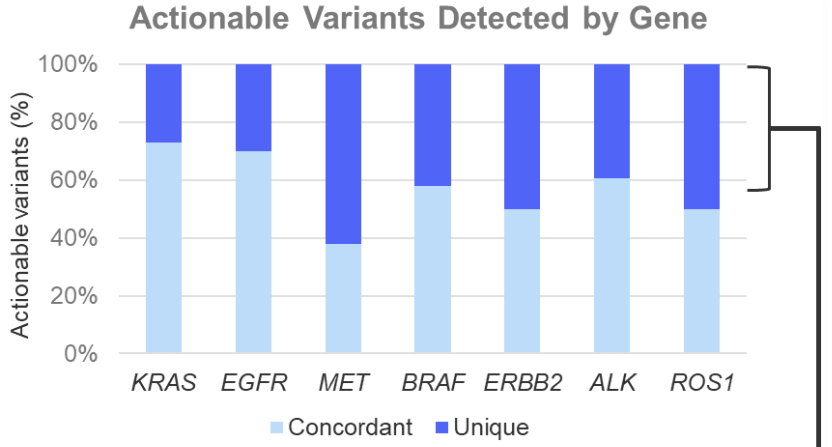
TAT=turn-around time

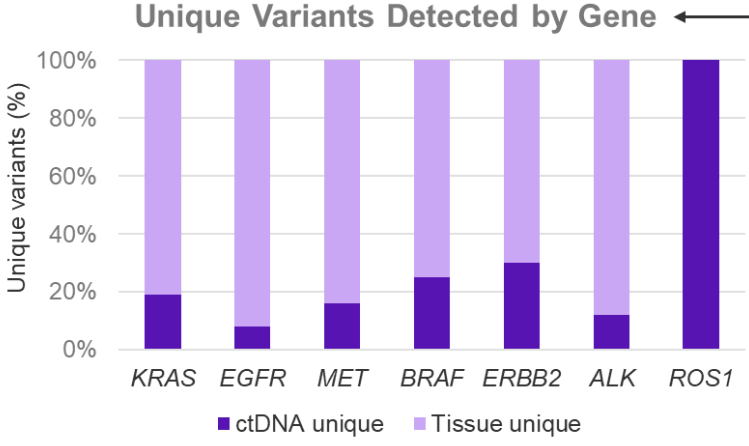
Gordon L, Diaz M, Patel A, et al. Abstract 1162P presented at ESMO 2022

Concurrent Biomarker Testing With Tissue and Liquid Biopsies Leads to Increased Detection of Actionable Variants









NSCLC: Non-small cell lung cancer; ctDNA: circulating tumor DNA

Iams WT, Mackay M, Ben-Shachar R, et al. *JAMA Netw Open*. 2024;7(1):e2351700

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Coverage & Reimbursement

Biomarker Testing for NSCLC

Companion Diagnostics (CDx) Claims

- ☑ are FDA approved by **demonstrating analytical and clinical validity** of the test through retrospective or prospective analyses, to accurately identify patients eligible to receive a targeted therapy for a defined biomarker

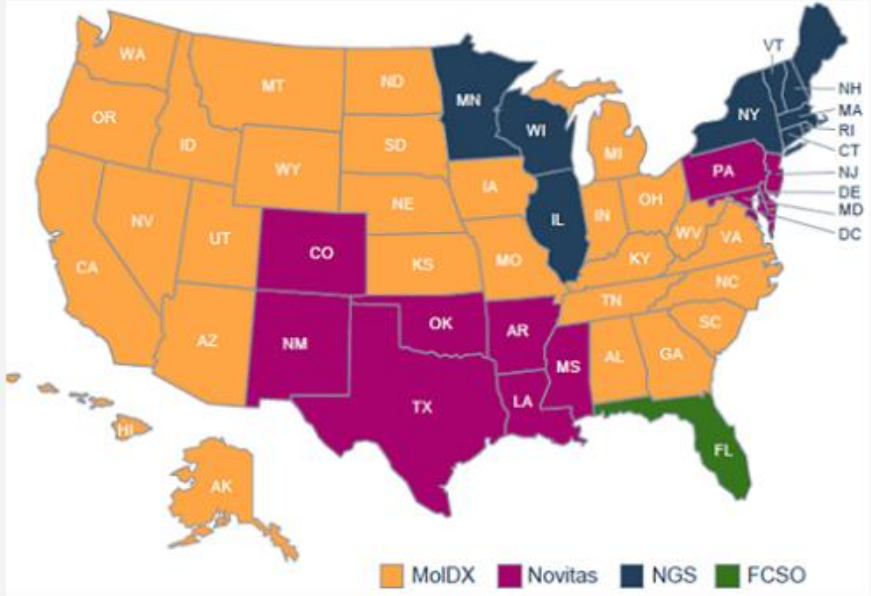
- ☑ are supported by **analytical validity** of the test for each specific biomarker **and a clinical study** establishing either the **link between the result of that test and patient outcomes or clinical concordance to a previously approved CDx test**

National Coverage Determination (NCD) 90.2 in a Nutshell

This National Coverage Determination (NCD) is only applicable to diagnostic lab tests using NGS for somatic (acquired) and germline (inherited) cancer.

For somatic testing:

- Only relapsed, refractory, recurrent, metastatic, advanced stage III or IV cancer
- Only panels predictive of drug response—no diagnostic or prognostic applications
- Requires FDA approval or clearance as a CDx
- Exclusive to NGS-based DNA panels—FISH, IHC, PCR excluded
- Is agnostic to liquid versus tissue; allows both since they are different tests
- MACs decide on payment for RNA-only tests, lab-developed tests, and MRD



Current states participating in the MolDX Program

Coverage of Tissue or ctDNA Testing in Advanced or Metastatic Cancer

Payer	CMP Coverage for tissue biopsy	Coverage for ctDNA	Allows for concurrent testing	Allows for repeat ctDNA testing
United Healthcare	CDx only	CDx OR <50 gene panels	Lung only	up to 3 times a year
Elevance (Anthem)	CMP for select tumors	CDx indications OR NSCLC, breast, and prostate*	No	Yes
Aetna	TMB only	Panels <50 genes for NSCLC	No	No
Cigna	CMP for select tumors	CDx only	No	No
Florida Blue	CDx only	CDX only	No	No
Horizon BCBS	CMP for select tumors	CDx only	No	No
BS CA	No limitations	covered for certain tumor types	Lung only	Not specified

Commercial Coverage Policy Examples

FDA Companion Diagnostic Testing medical coverage policy
CDx tests are proven and medically necessary when the oncology indication has a corresponding diagnostic test and biomarker on the US FDA list of cleared or approved Companion diagnostic devices. (Agnostic to tissue or liquid.)

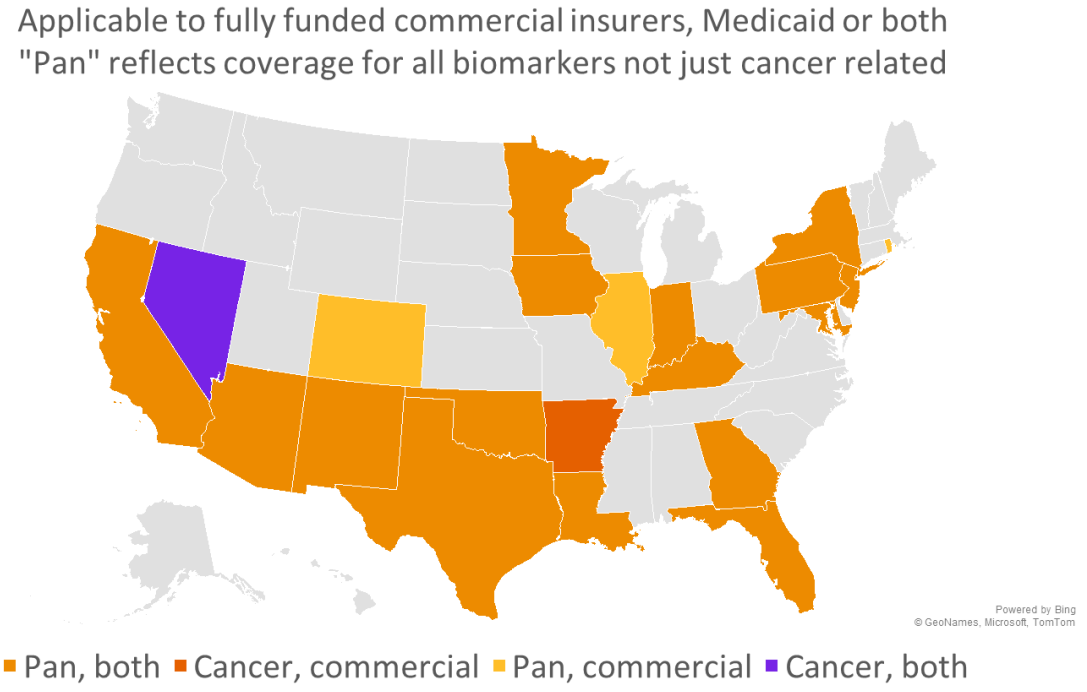
Tumor Markers medical coverage policy
Circulating tumor DNA (ctDNA) (a type of liquid biopsy) for any indication (other than small panels, less than 50 genes, for non-small cell lung cancer), including, but not limited to, colorectal cancer, melanoma, ovarian cancer or prostate cancer are **considered experimental and investigational.**

Footnote

ACS/CAN Biomarker Testing Bill Coverage in the US

Biomarker testing must be covered when the test is supported by medical and scientific evidence, including, but not limited to:

- Labeled indications for an FDA-approved or -cleared test;
- Indicated tests for an FDA-approved drug;
- Warnings and precautions on FDA-approved drug labels;
- CMS National Coverage or Medicare Administrative Contractor (MAC) Local Coverage of a test; or
- Nationally recognized clinical practice guidelines (and consensus statements).



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Q&A

Thank you for attending!