Complementary Liquid Biopsy in Lung Cancer: More is not Necessarily Better

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Introduction

- Molecularly targeted therapies have had a significant impact on outcome in patients with metastatic NSCLC
- Timely testing and administration of appropriate medications are essential.
- Tissue-based testing has been the standard of care for many years
- Circulating tumor DNA (also known as liquid biopsy) is gaining ground

Liquid Biopsy Advantages

- Easy access
- Rapid turn around time
- Might reflect tumor heterogeneity
- Can be done serially for follow up

Does complementary liquid biopsy make a significant difference?

- Does the proposed testing detect a significantly higher number of mutations in newly diagnosed patients with metastatic NSCLC?
- Does detecting more mutations translate to better outcomes?
- Is the benefit worth the additional financial burden?

Precision Medicine and Imaging

Clinical Cancer Research

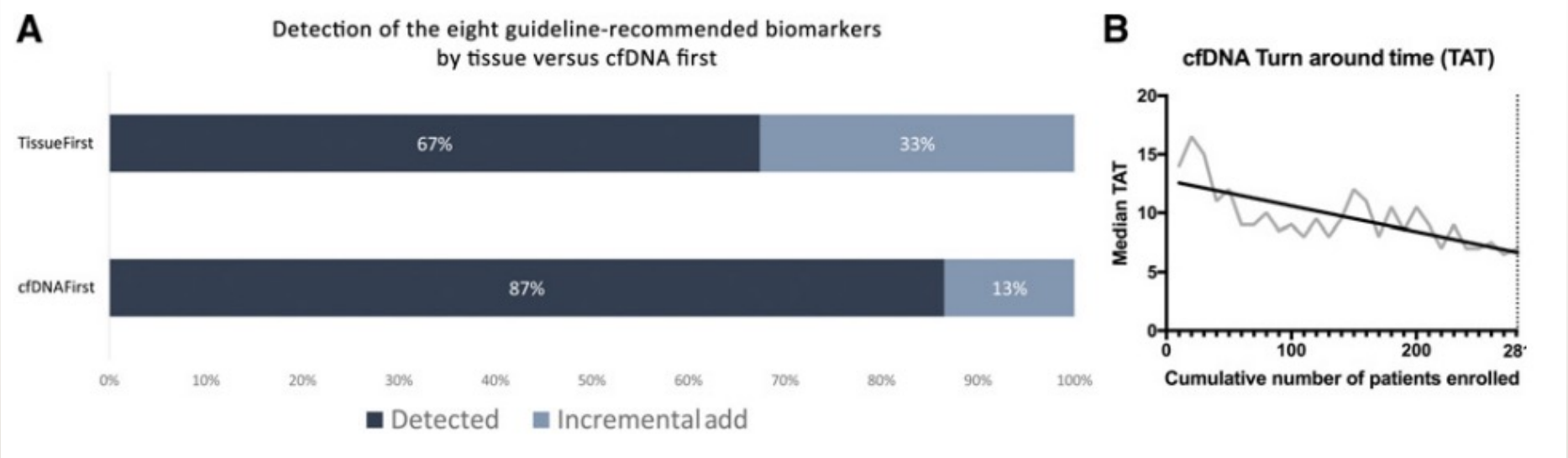
Clinical Utility of Comprehensive Cell-free DNA Analysis to Identify Genomic Biomarkers in Patients with Newly Diagnosed Metastatic Non–small Cell Lung Cancer

Natasha B. Leighl[1], Ray D. Page[2], Victoria M. Raymond[3], Davey B. Daniel[4], Stephen G. Divers[5], Karen L. Reckamp[6], Miguel A. Villalona-Calero[7], Daniel Dix[3], Justin I. Odegaard[3], Richard B. Lanman[3], and Vassiliki A. Papadimitrakopoulou[8]

NILE Study:

- 282 non-squamous NSCLC patients accrued from 28 North American centers
- Patients had routine genotyping as per local oncologists' SOC and liquid biopsy was sent on all patients
- Guideline-recommended biomarkers were identified in 60 patients by tissue and in 77 patients by cfDNA (21.3% vs. 27.3%)

Leighl et al. Clin Cancer Res 2019;25:4691–700

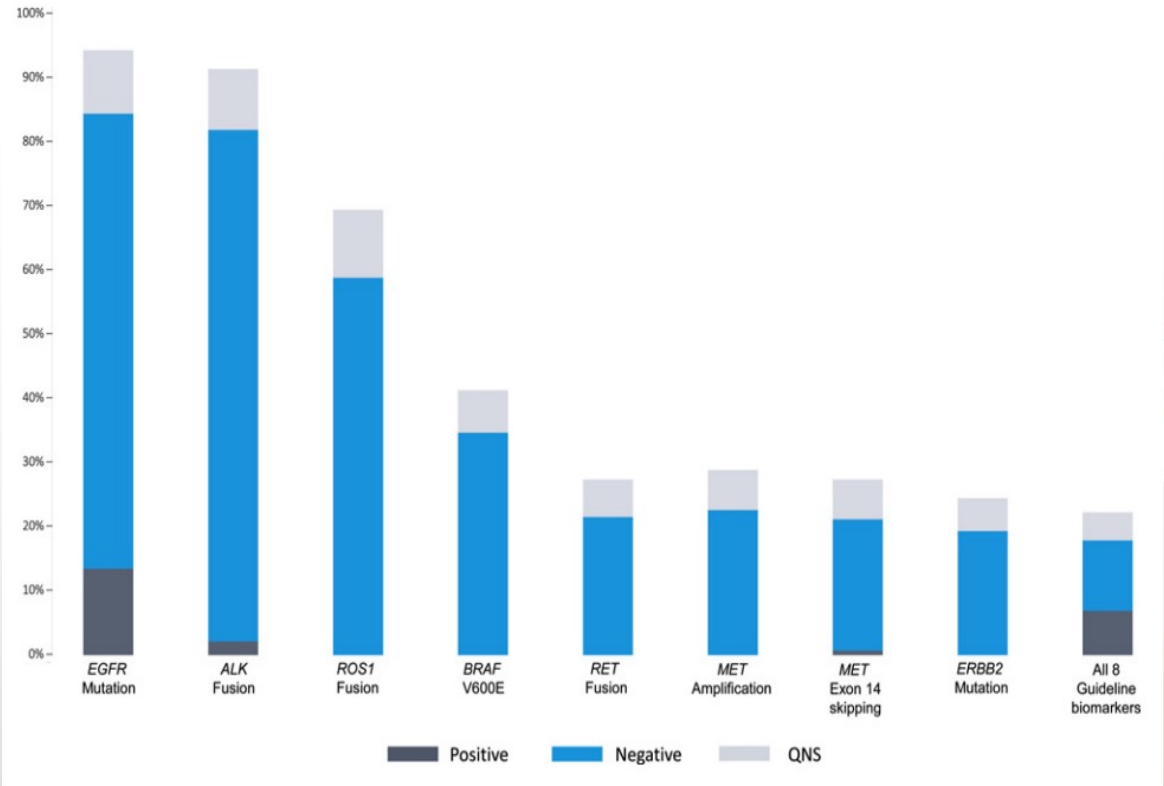


Leighl et al. Clin Cancer Res 2019;25:4691–700

Limitations

- Routine NGS testing on tissue specimens was not done. Testing in most patients was done sequentially for individual mutations using various methods.
- Only 51 (18.1%) patients had tissue tested for all 8 recommended genes.
- Most of mutations detected by cfDNA but not in tissue specimens were because either the tissue specimen did not have enough tissue, or the mutation was not tested for to begin with.

Leighl et al. Clin Cancer Res 2019;25:4691–700



Guideline-recommended biomarker positivity by sample type in patients with attempted/completed genotyping for all eight biomarkers

		Tissue		
		Positive	Negative	Total
cfDNA	Positive	19	3	22
	Negative	3	39	42
	Total	22	42	64

Leighl et al. Clin Cancer Res 2019;25:4691–700

IJBM The International Journal of Biological Markers

Original Research Article

Comparison of the somatic mutations between circulating tumor DNA and tissue DNA in Chinese patients with non-small cell lung cancer

The International Journal of Biological Markers
1–9

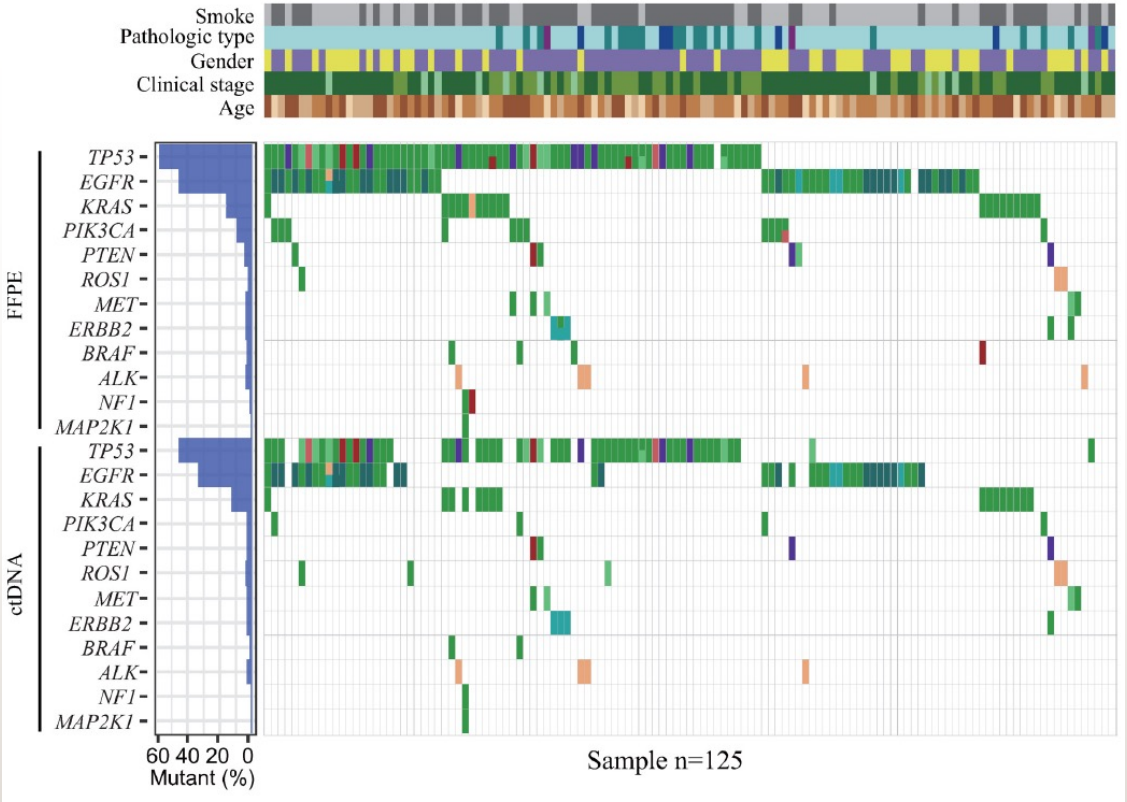
DOI: 10.1177/03936155221099036
journals.sagepub.com/home/ijbm
SAGE

Meng Zhang[1], Yi Feng[1], Changda Qu[1], Meizhu Meng[1], Wenmei Li[1], Meiying Ye[1], Sisi Li[1], Shaolei Li[2], Yuanyuan Ma[2], Nan Wu[2] and Shuqin Jia[1]

- 125 patients with NSCLC who underwent routine NGS-based tissue and plasma mutation testing at a CLIA-CAP accredited testing facility in China.

- Concordance rate between plasma and tissue was 98.4%:
  - 118 concordant mutations in 70 patients
  - 50 discordant mutations in 25 patients
    - Most discordant mutations were detected in tissue only
    - Only one patient had a discordant mutation in plasma only

Zhang et al. Int J Biol Markers. 2022 July (Epub)



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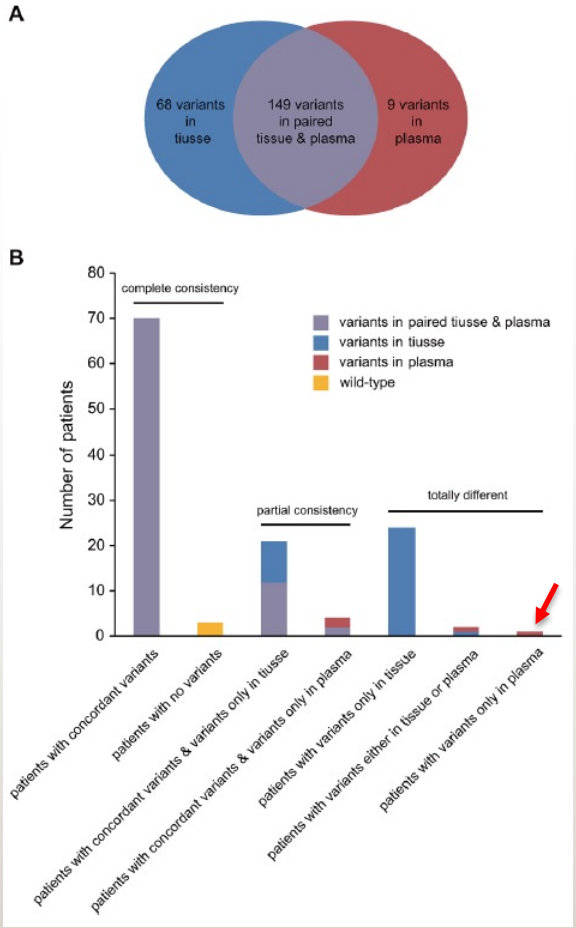

Zhang et al. Int J Biol Markers. 2022 July (Epub)

frontiers | Frontiers in Oncology

ORIGINAL RESEARCH
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doi: 10.3389/fonc.2022.912801

Liquid First Is "Solid" in Naïve Non-Small Cell Lung Cancer Patients: Faster Turnaround Time With High Concordance to Solid Next-Generation Sequencing

Or Sehayek[1†], Waleed Kian[2†], Amir Onn[3], Ronen Stoff[3], Hadas Gantz Sorotsky[3], Melanie Zemel[1], Jair Bar[3], Yulia Dudnik[4], Hovav Nechushtan[5], Yakir Rottenberg[5], Lior Soussan-Gutman[6], Addie Dvir[6], Laila C. Roisman[2‡] and Nir Peled[2*‡]

- 42 consecutive patients with NSCLC who underwent routine tissue-based testing (not necessarily NGS) and plasma mutation testing using Guardant360 CDx.

- 5 patients did not have enough tissue for full tissue-based profiling.
- 18 mutations were identified in 17 patients:
  - 11 mutations detected by both techniques
  - 3 mutations were detected in tissue only
  - 4 mutations were detected in plasma only (1 *ROS1*, 2 *MET*, 1 *RET*)

Sehayek et al. Front. Oncol. 12:912801.

Clonal Hematopoiesis:

- 10% of people > 65 years of age had detectable evidence of clonal hematopoiesis of unknown significance.
- Most commonly in *TP53* and *KRAS*

Genovese et al. NEJM 2014,371:2477-2487

Any evidence for improved outcome?

- Only the NILE study reported on response rates.

- 282 patients enrolled
  - 89 patients identified as having a mutation
  - 61 patients received a targeted agent
  - 33 patient were identified as having RECIST-evaluable disease

		Number (N = 33)	Percent
Overall response	CR	1	3
	PR	18	55
	SD	12	36
	PD	2	6
Best overall response (BOR)	CR + PR	19	58
Disease control rate (DCR)	CR + PR + SD	31	94
Durable response at 6 months	CR + PR + SD	25	76
Event-free survival at 12 months	CR + PR + SD	17	52
EGFR BOR	CR + PR	13	50
	Common EGFR (Exon19, L858R)	12	92
	EGFR rare (G719A, L833V)	1	8
	Germline EGFR T790M	0	0
ALK BOR	CR + PR	6	100
ROS1 BOR	CR + PR	0	0

What about cost?

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ORIGINAL RESEARCH
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Economic Analysis of Tissue-First, Plasma-First, and Complementary NGS Approaches for Treatment-Naïve Metastatic Lung Adenocarcinoma

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Monetary loss=testing cost + time cost

Time cost= time x average wage

Yang et al. Front. Oncol. 12:873111.

	Cost (US$)	Time (day)	Monetary loss[b] (US$)	Patients with appropriate FDA-approved therapies
"Tissue-first" NGS approach	2354 (1963 to 2779)	15.3 (12.9 to 18.0)	4745 (4010 to 5480)	99.4% (98.9 to 99.8%)
"Complementary" NGS approach	4795 (4085 to 5453)	12.7 (10.8 to 14.9)	6778 (5923 to 7600)	99.4% (98.9 to 99.8%)
"Plasma-first" NGS approach	4316 (3659 to 4946)	17.2 (14.7 to 20.1)	7006 (6047 to 7964)	99.4% (98.9 to 99.8%)

Yang et al. Front. Oncol. 12:873111.

#9128

Molecular Testing and Patterns of Treatment in NSCLC Patients: An IASLC Analysis of ASCO CancerLinQ Discovery Data

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Background

- Precision medicine has resulted in improved outcomes for non-small cell lung cancer (NSCLC)
- While molecular testing is considered critical for guiding treatment decisions for advanced stage NSCLC, adoption of testing in routine practice is variable
- We analyzed the factors contributing to molecular testing and treatment patterns in patients with lung cancer

Methods

- The ASCO CancerLinQ Discovery dataset was queried to identify patients diagnosed with lung cancer between the years 2010-2018
- Data on demographics, tumor stage, histology and treatments were extracted, and receipt of molecular testing was investigated as the primary outcome
- Univariate association of clinicopathological variable with molecular testing outcome was performed. A multivariable logistic regression analysis with backward selection at an alpha of 0.05 was reported

Methods

- NSCLC patients with stage IV disease were included in this analysis
- A subgroup analysis was performed for patients with adenocarcinoma histology subtype
- Molecular testing for patients was determined using the laboratory code labels that included individual gene level tests, fusion/rearrangement testing, large-scale genomic testing. The code labels which indicated a genomic/genetic result for patients were identified and included in the analysis

Results

- A total of 37,925 NSCLC patients with stage IV disease were analyzed
- Patient characteristics: median age 65 years, 51% male, 68% white, 33.5% adenocarcinoma
- About 22% of all stage IV NSCLC patients had molecular testing results
- In adenocarcinoma patients, 49% had molecular testing results available

Conclusion

In the analysis of large real-world dataset of stage IV NSCLC patients, white race and female sex are associated with higher likelihood of having molecular test performed. The percentage of patients undergoing testing remains sub-optimal.

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Results

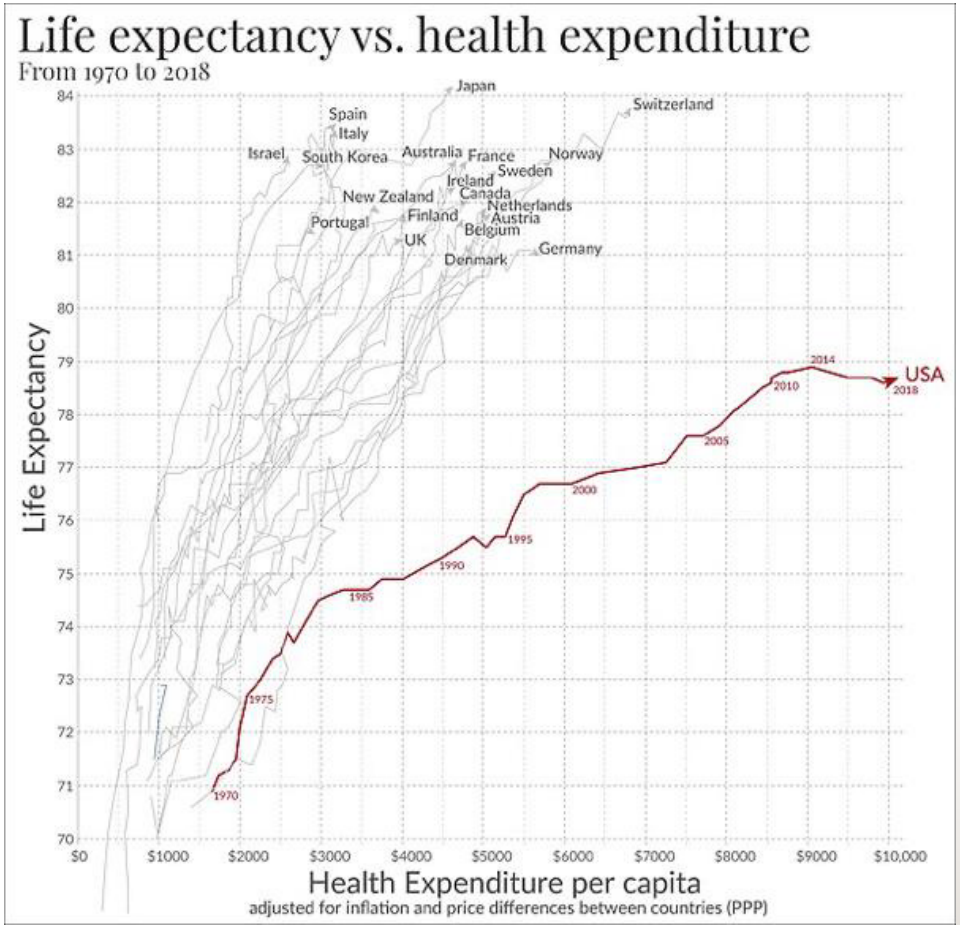
- In the stage IV group, 47% were treated with chemotherapy, 16% with immunotherapy and 3% with targeted therapy
- MVA of factors associated with receipt of molecular testing shown in the tables.
- These results were also confirmed on a subgroup analysis of adenocarcinoma patients

Molecular Testing= Yes

Covariate	Level	N	Odds Ratio (95% CI)	OR *p*-value
Gender	Female	18583	1.29 (1.22-1.37)	<.001
	Male	19339	-	-
Race	Black or African American	5620	0.89 (0.81-0.97)	0.009
	Asian	573	2.22 (1.79-2.75)	<.001
	White	25708	-	-
Ethnicity	Hispanic or Latino	869	1.24 (1.02-1.52)	0.030
	Unknown	13201	0.52 (0.49-0.56)	<.001

Molecular Testing= Yes

Covariate	Level	N	Odds Ratio (95% CI)	OR *p*-value
Received Immunotherapy?	Yes	5968	1.86 (1.72-2.01)	<.001
	No	31954	-	-
Received Targeted Therapy?	Yes	1172	2.29 (2.00-2.64)	<.001
	No	36750	-	-
Received Chemotherapy?	Yes	17692	1.39 (1.30-1.48)	<.001
	No	20230	-	-


Life expectancy vs. health expenditure
From 1970 to 2018
Japan
Switzerland
Spain
Italy
Israel
South Korea
Australia
France
Norway
Sweden
Ireland
Canada
New Zealand
Netherlands
Portugal
Finland
Austria
Belgium
UK
Germany
Denmark
USA
1970
1975
1985
1990
1995
2000
2005
2010
2014
2018
Life Expectancy
84
83
82
81
80
79
78
77
76
75
74
73
72
71
70
$0
$1000
$2000
$3000
$4000
$5000
$6000
$7000
$8000
$9000
$10,000
Health Expenditure per capita
adjusted for inflation and price differences between countries (PPP)

STATE OF THE ART: CONCISE REVIEW

Liquid Biopsy for Advanced NSCLC: A Consensus Statement From the International Association for the Study of Lung Cancer

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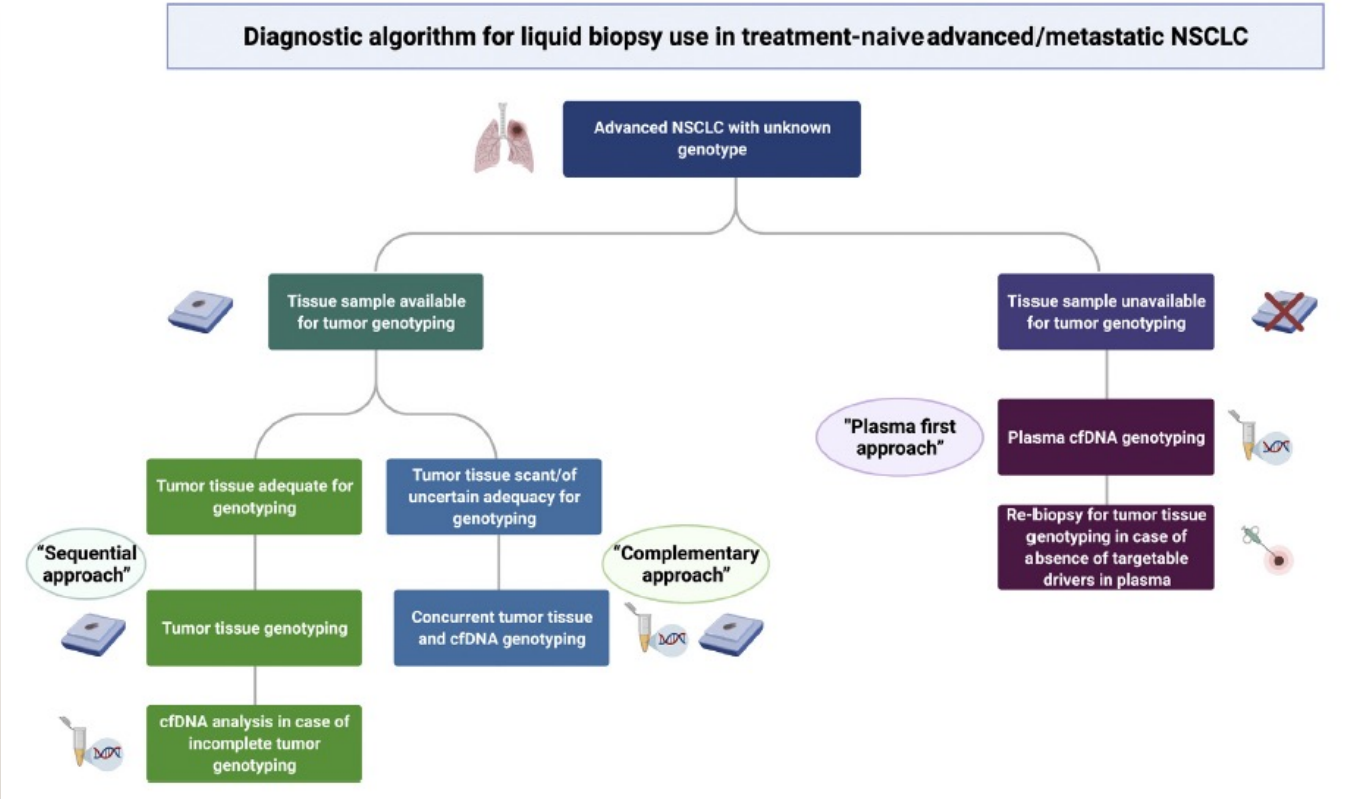

Rolfo et al. Journal of Thoracic Oncology Vol. 16 No. 10: 1647–1662