UC San Diego Health

Biomarkers in lung cancer: state of the art

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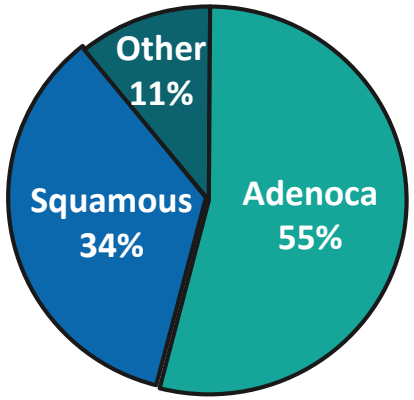
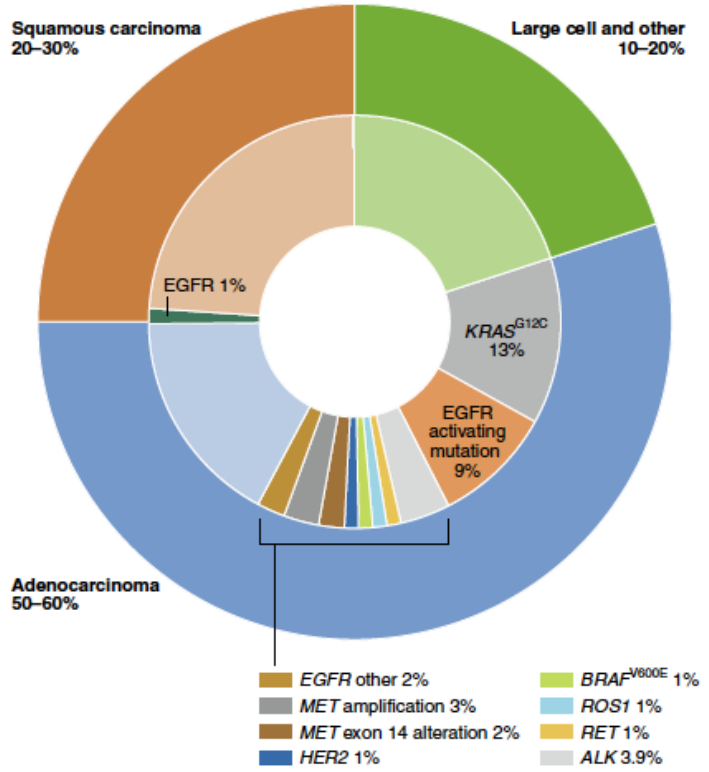
NSCLC: Not One Disease, But Many

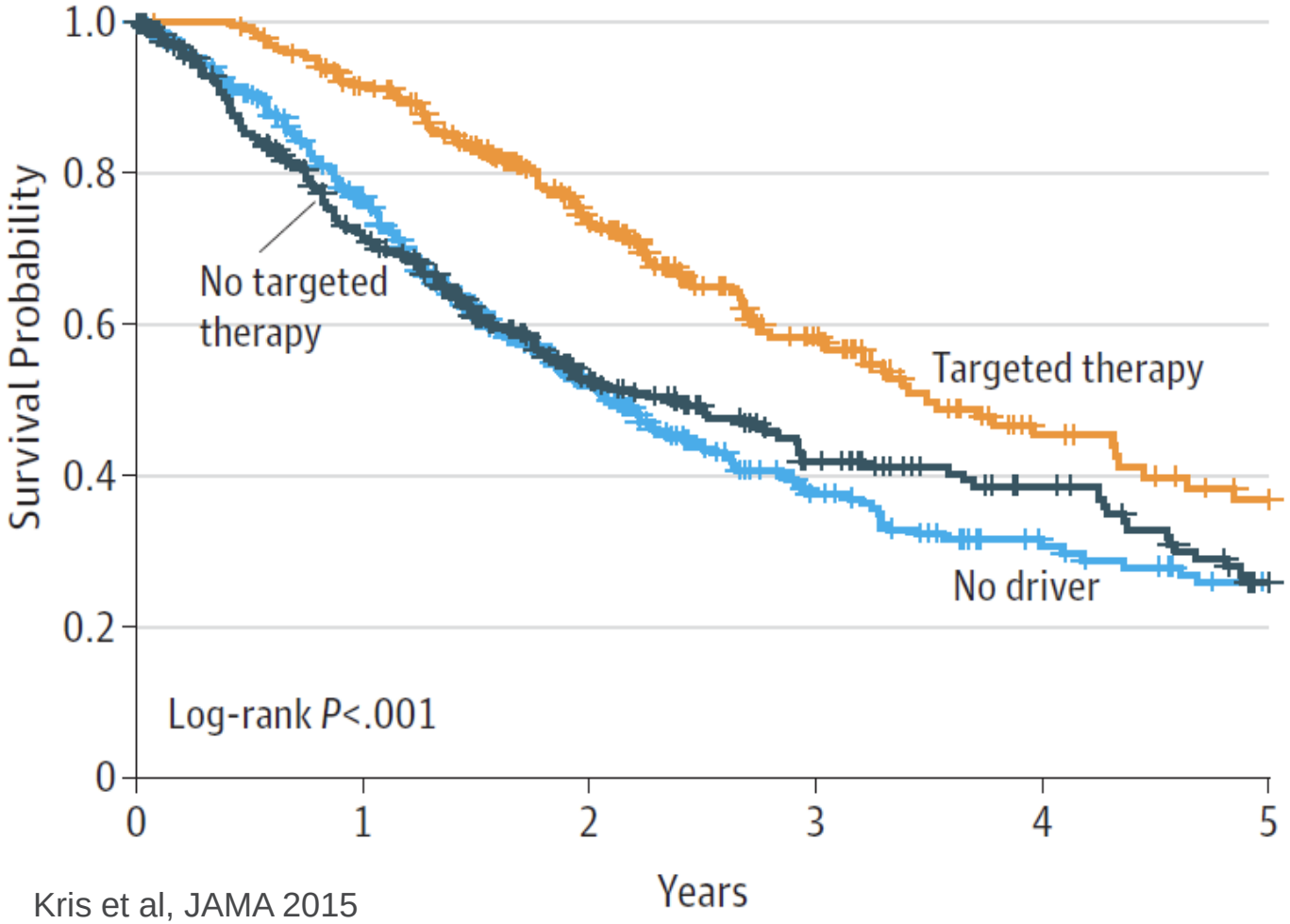




Then — Histology-Based Subtyping — Now

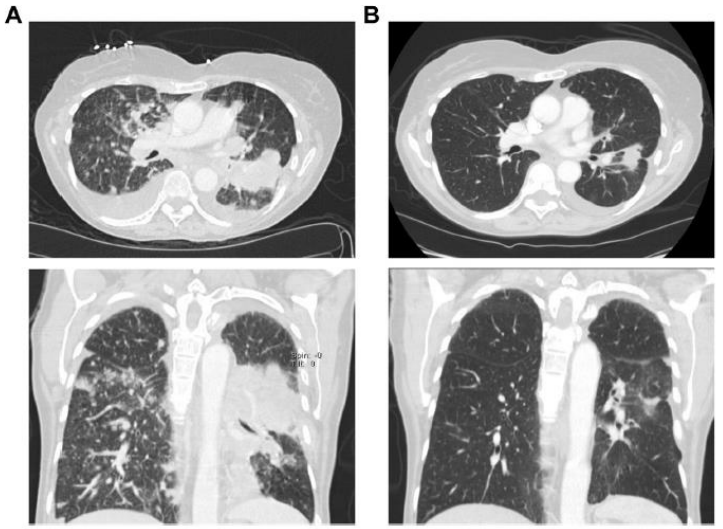
Wang et al, Nature Medicine 2021

Treating Patients with Oncogenic drivers with targeted therapy improves overall survival



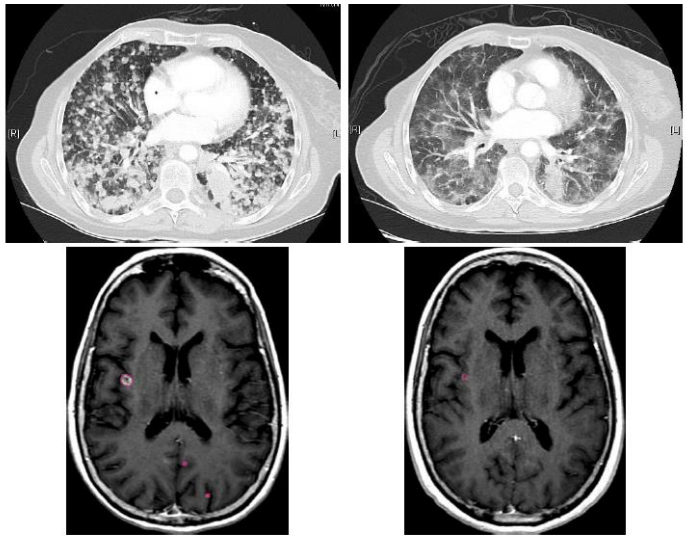
Kris et al, JAMA 2015

ROS 1 rearrangement and crizotinib at 6 weeks



Lin et al JTO 2017

NTRK rearrangement and larotrectinib at 2 months

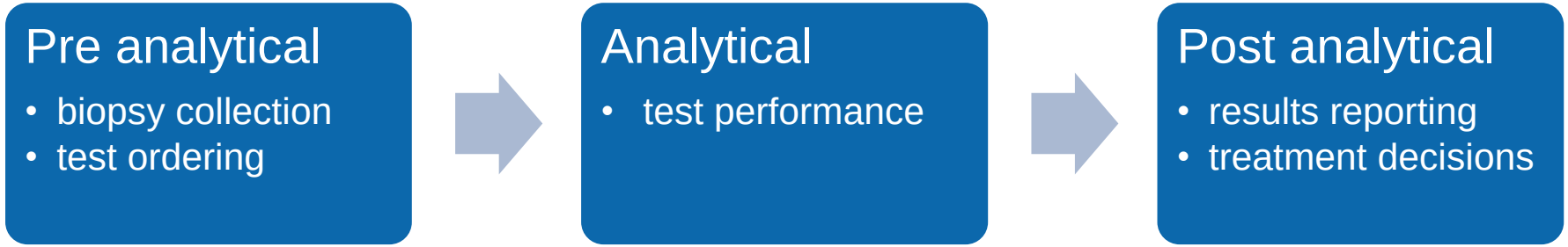


Lassen et al ESMO 2018

Pitfalls in biomarker testing

- Biomarker testing rates
- Disparities in biomarker testing
- Challenges in ordering correct biomarkers
- Challenges in interpreting biomarkers in lung cancer

Biomarker testing in NSCLC



- Multiple steps from diagnosis to treatment
  - operational inefficiencies
  - limited awareness or understanding of biomarker strategies
  - inappropriate use of testing results
  - coverage and payment challenges

Pre analytical

Biomarker testing rates

Retrospective analysis performed at OneOncology, a network of multidisciplinary, research-focused community practices using Flatiron Database

A total of 3,860 patients with aNSCLC were included:

3,221 (83%) patients had ≥ 1 biomarker test (*ALK*, *BRAF*, *EGFR*, *KRAS*, *PD-L1* and *ROS-1)*

- 2,045 (63%) patients received NGS with or without other biomarker tests
- 639 (17%) patients did not receive biomarker testing
- Of 1,207 patients with aNSCLC with actionable mutations, 390 (32%) received treatment before receiving their biomarker test results

Figure 4. Trends of Treatment Patterns Prior to Receiving Biomarker Test Results

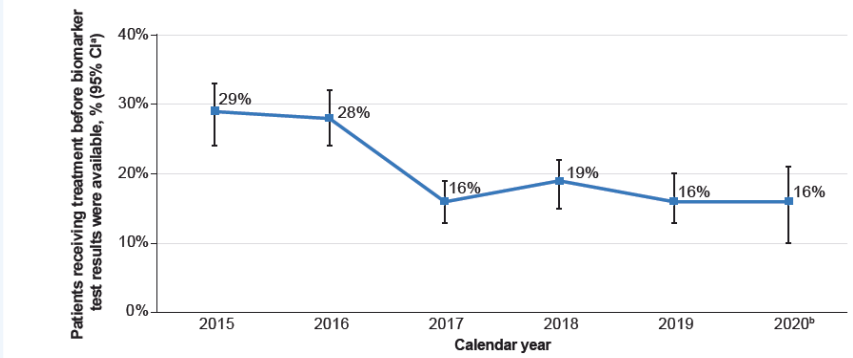


Figure 2. Testing Rates for All 6 Selected aNSCLC Biomarkers[a] Over Time

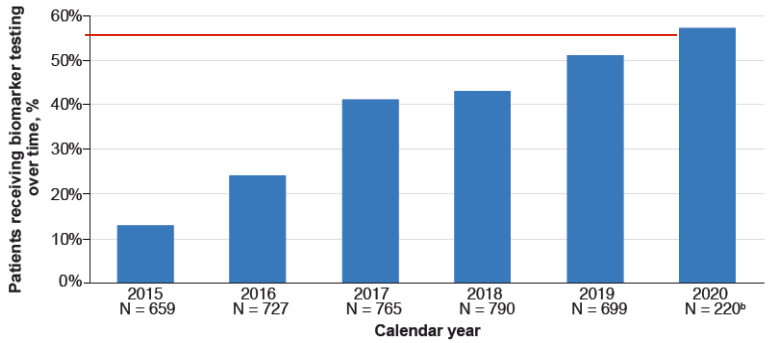
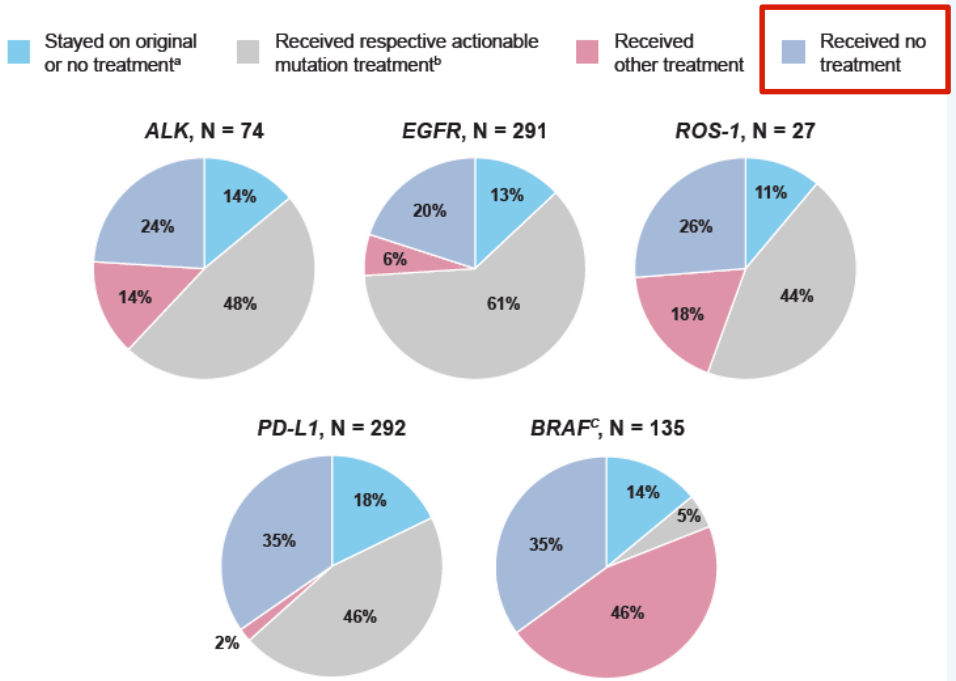


Figure 5. Treatment Strategies Following Biomarker Test Results by Actionable Mutations



VanderWalde et al, ASCO Quality Care Symposium 2021

Impact of clinical practice gaps.

Potential practice gaps	Step 1	Step 2			Step 3		Step 4		Step 5		Step 6	Step 7
	Tissue and/or liquid biopsy not performed	Tissue sufficiency: Initial biopsy	Tissue sufficiency: Rebiopsy	Insufficient tumor	Tumor load overestimation		Physicians not ordering testing; Lack of awareness of current guidelines for NSCLC testing; Insurance challenges	Premature treatment initiation	No results reported (QNS/TNP/ inconclusive rates)	Test performance /sensitivity	TAT – result not reported within treatment decision window	Targeted treatment not selected despite positive test result; Report indicates alternative/no therapy
Data sources	Medicare claims data SEER data	Medicare claims data Published journals			Medicare claims data Published journals		Medicare claims data Published journals Real-time laboratory data		Medicare claims Real-time laboratory data Published journals		Medicare claims data	CMS Claims data (parts A, B and D) Real-time laboratory data Published journals
Patients available	1000	934			798		784		642		524	503
% of patients lost	6.6	4.0	0.97	9.6	0	1.7	17.5	0.6	14.5	3.9	4	29.2
Patients advancing	934	798			784		642		524		503	356
Total patients lost	**66**	**136**			**14**		**142**		**118**		**21**	**147**

Sadic et al JCO Precision Oncology 2022

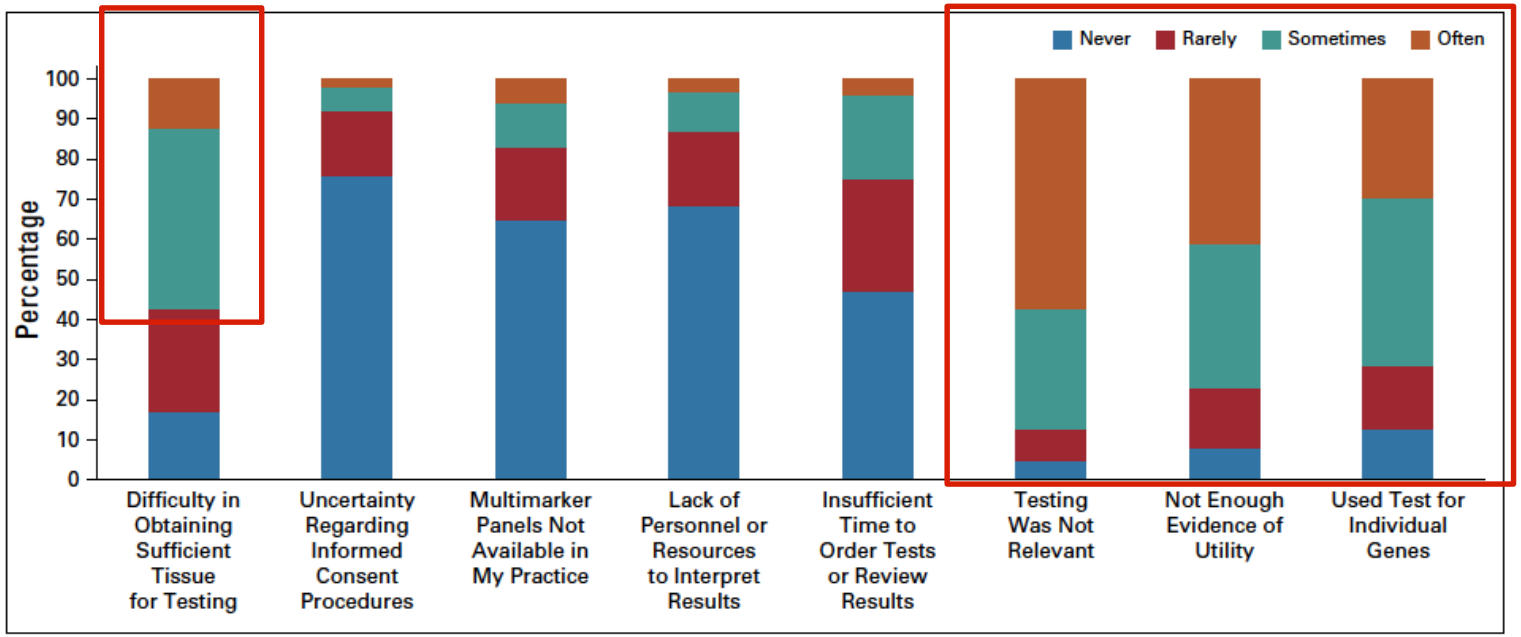
Testing disparities

- Retrospective cohort study January 2017-October 2020. Flat Iron Electronic database (800 sites of care)
- 14768 patients.
  - 68% white, 8.7 % black/AA, 3.2% Asian. 11% unknown
  - Black/AA patients are less likely to undergo biomarker testing and less likely to have NGS
  - Reasons are not clear (institutional differences, other SE determinants of health, insurance)

All patients with NSCLC				
	NSCLC overall N=14,768	White N=9,793	Black/AA N=1,288	P-value, White vs Black/AA
Ever tested	11,297 (76.5%)	**7477 (76.4%)**	**948 (73.6%)**	**0.03**
Tested prior to first line therapy		6,064 (61.9%)	784 (60.9%)	0.47
Ever NGS tested	7,185 (48.7%)	**4,904 (50.1%)**	**513 (39.8%)**	**<0.0001**
NGS tested prior to first line therapy		**3,081 (31.5%)**	**332 (25.8%)**	**<0.0001**
Patients with non-squamous NSCLC				
	Non-squamous N=10,333	White N=6,705	Black/AA N=922	P-value, White vs Black/AA
Ever tested	8,786 (85.0%)	5,699 (85.0%)	764 (82.9%)	0.09
Tested prior to first line therapy		4,881 (72.8%)	662 (71.8%)	0.52
Ever NGS tested	5,494 (53.2%)	**3,668 (54.7%)**	**404 (43.8%)**	**<0.0001**
NGS tested prior to first line therapy		**2,452 (36.6%)**	**274 (29.7%)**	**<0.0001**

Bruno et al ASCO 2021 abs 9005

Having support infrastructure is important

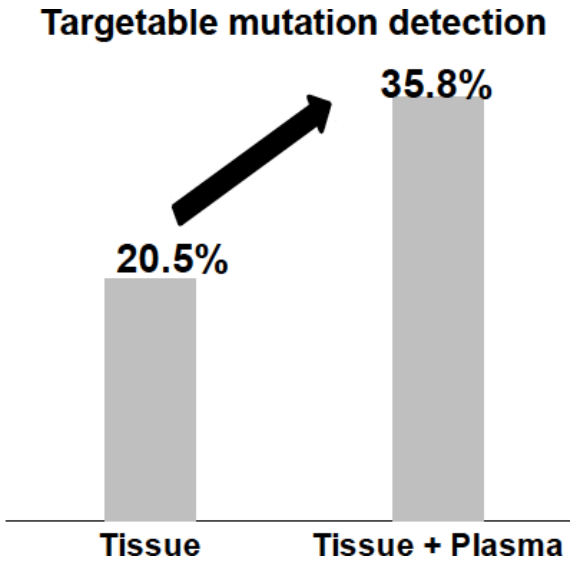


- 1286 medical oncologists surveyed. (return rate 38%)
- Survey took place in 2017
- Mixture of solid and liquid tumors
- 62% affiliated with academic institutions.
- Working or being associated with academic institutions, having on site pathology, **internal genomic testing policies,** and onsite genetic counselors were less likely to report difficulties with obtaining molecular testing

Roberts et al JCO Precision Oncology 2021

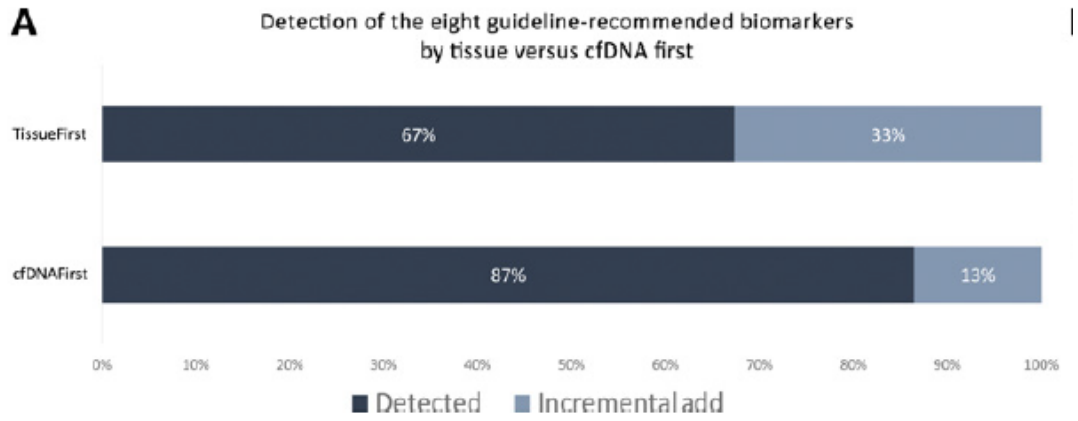
Analytical

Tissue first or liquid first or both



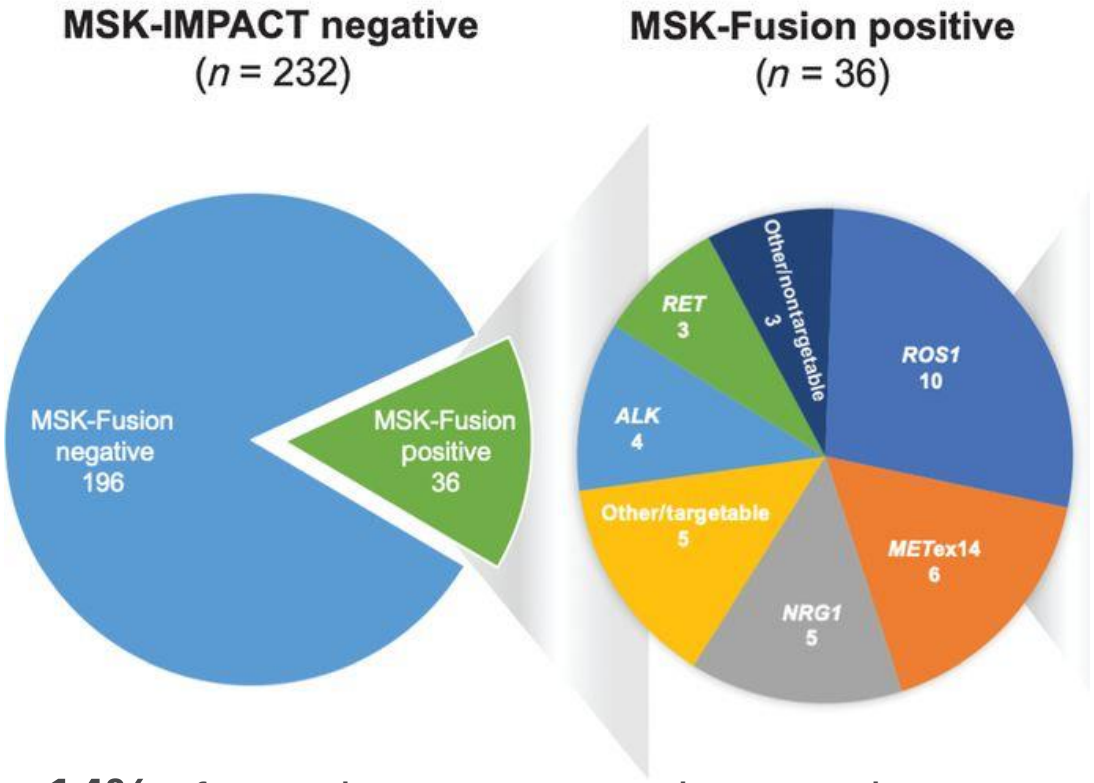
FN rate of ctDNA 20-30%

Guideline-recommended biomarker positivity by sample type		Tissue		
		Positive	Negative	Total
cfDNA	Positive	48	29	77
	Negative	12	193	205
	Total	60	222	282



LeighlNB, et al. Clin Cancer Res. 2019;25(15):4691-4700.
Aggarwal C et al., JAMA Oncology , 2018

DNA vs RNA



14% of tested DNAseq-negative samples were positive by for fusions or rearrangements by RNAseq.

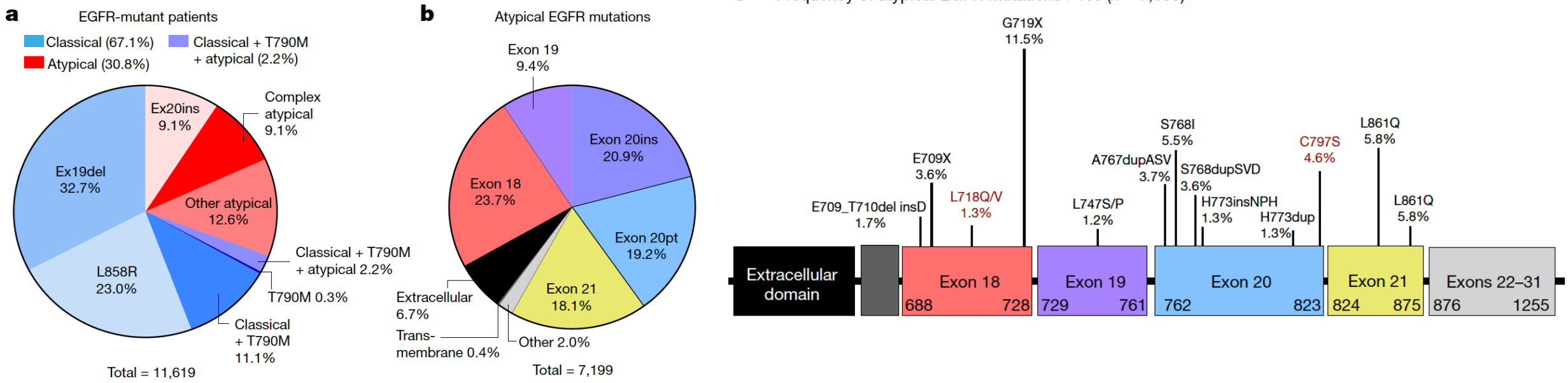
- Lung adenocarcinoma cases lacking an oncogenic activating mutation in BRAF, EGFR, NRAS, KRAS, ERBB2, MAP2K1, MET; amplification of EGFR, ERBB2, FGFR1, MET; fusions in ALK/ RET/ROS, NTRK1/2/3, NRG1, BRAF analyzed by MSK-Fusion panel (RNAseq).
- 1,933 of 2,522 cases were positive for oncogenic drivers using MSK-IMPACT.
- 589 were subjected to sequencing.
  - 232 sequenced
- RNA from the available driver-negative cases (*n* = 232) was tested using the MSK-Fusion panel.
  - Gene fusions (*n* = 29), *METex14* mutations (*n* = 6), and *EGFRvIII* (*n* = 1) were detected.

 Benayed et al, Clinical Cancer Research 2019,

Post analytical

Article

Structure-based classification predicts drug response in *EGFR*-mutant NSCLC



Robichaux JP et al. *Nature* **597**, 732–737 (2021).

Testing is important before initiating 1L IO

IMMUNOTARGET Registry

	EGFR N=125		KRAS N=271		ALK N=23		BRAF N=43		ROS1 N=7	
PDL1 Status available	N = 49		N = 95		N = 11		N = 10		N = 5	
PDL1 Status										
Negative	18	36.7%	32	33.7%	4	36.4%	3	30%	0	0%
Positive (>1%)	31	63.3%	63	66.3%	7	63.6%	7	70%	5	100%
% of tumor cells										
PDL1 staining <10%	21	55.3%	39	48.8%	5	50%	3	33.3%	0	0%
≥10%	17	44.7%	41	51.3%	5	50%	6	66.7%	5	100%
missing	11		15		1		1		0	
% of tumor cells										
PDL1 staining <50%	27	71.1%	54	67.5%	6	60%	4	44.4%	2	40%
≥50%	11	28.9%	26	32.5%	4	40%	5	55.6%	3	60%
missing	11		15		1		1		0	
% of tumor cells PDL1 positive										
Median	3.5		12.5		7.5		50		90	
Range	0-90		0-100		0-90		0-90		20-100	
missing	11		15		1		1		0	

Mazieres J,. Ann Oncol. 2019 .

Mutation trumps PD-L1

Driver	n	RR	PFS	OS	Impact (+/-) on PFS of				Comments
					PDL1	Smoking	Nb line	Subtype	
Total		19%	2.8	13.3					Outcome consistent with registration trials for ICI
KRAS	271	26%	3.2	13.5	+	X	X	X	Clear benefit across all subgroups
EGFR	125	12%	2.1	10	+	X	X	+/-(1)	Could be considered in PDL1 + after TKIs exhaustion
BRAF	43	24%	3.1	13.6	NA	+	X	X	Could be considered in smokers
MET	36	16%	3.4	18.4	NA	X	NA	X	Could be considered after conventionnal treatment
HER2	29	7%	2.5	20.3	NA	+	X	NA	
ALK	23	0	2.5	17	NA	-	X	NA	Poor outcome. New biomarker needed.
RET	16	6%	2.1	21.3					
ROS1	7	17%	-	-					

+ : positive impact on PFS
X : non-significant impact on PFS
- : negative impact on PFS
(1) Depending on the mutation subtype, cf. table A7

Mazieres, Annals of oncology 2019

Word of Caution About Immunotherapy

- Patients with EGFR mutations have traditionally been excluded from all 1L chemo/IO and IO trials with an exception of IMPOWER 150 (had to fail TKI)
- No randomized trials comparing chemo/IO vs EGFR TKI
  - Randomized trials comparing platinum doublet vs 1st and 2nd gen TKI strongly favor TKI
- Response rates and PFS to IO monotherapy is low in 2L trials
- Potential increased toxicity if IO is given before TKI
  - Lisberg et al: ORR of 0% in 10 PD-L1+ (7 w PD-L1>50%), EGFR-mutant, TKI naive patients; 1 fatal pneumonitis after TKI
  - Schoenfeld et al: 15% of patients (6 of 41) who received ICI followed by osimertinib developed a severe irAE

Lisberg A et al. *J Thorac Oncol.* 2018;13(8):1138-1145; Schoenfeld AJ et al. *Ann Oncol*. 2018;30(5):839-844.

Hepatotoxicity associated with ALK TKI after ICI vs TKI Alone

Table 2. Increase in ALT/AST Level with Crizotinib after an ICI versus with Crizotinib Alone

	Patients, n		Cumulative Incidence of Liver Toxicity		
Increase in ALT/AST Level	Total	Liver Toxicity	Point Estimate, %	(95% CI)	*p* Value
Grade 3/4 increase in ALT level					<0.0001
ICI → TKI	11	5	45.5	(14.9-72.2)	
TKI	442	34	8.1	(5.7-11.0)	
Grade 4 increase in ALT level					<0.0001
ICI → TKI	11	3	27.3	(5.8-55.4)	
TKI	442	4	0.9	(0.3-2.2)	
Grade 3/4 increase in AST level					<0.0001
ICI → TKI	11	4	36.4	(10.0-64.2)	
TKI	442	14	3.4	(1.9-5.5)	
Grade 4 increase in AST level					<0.0001
ICI → TKI	11	3	27.3	(5.8-55.4)	
TKI	442	1	0.2	(0.02-1.3)	

Note: Grading is per the Common Terminology Criteria for Adverse Events, version 4.0.
Point estimate is reported at the time of last observed event.
ALT, alanine transaminase; AST, aspartate transaminase; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; CI, confidence interval.

Lin et al JTO 2019

Challenges in delivering precision medicine

1. **Testing is not ordered on all the patients.**
    - education of physicians and patients, testing pathways, elimination of disparities
2. **Testing is not performed due to limited tumor samples**
    - encourage multiplex testing, core biopsy, multidisciplinary approach to tissue stewardship (establish workflow within you institution that secures adequate tissue at the time of acquisition and before tissue send out), Avoid unnecessary IHC stains
    - ctDNA (be aware of false negative rate)
3. **Once performed test results are not leading to an appropriate therapy**
    - understand molecular biology, different testing methods (IHC positivity might not mean the same as mutation presence), variants of unknown significance, system improvement in following molecular results (EMR integration).