Liquid biopsy and Precision Oncology

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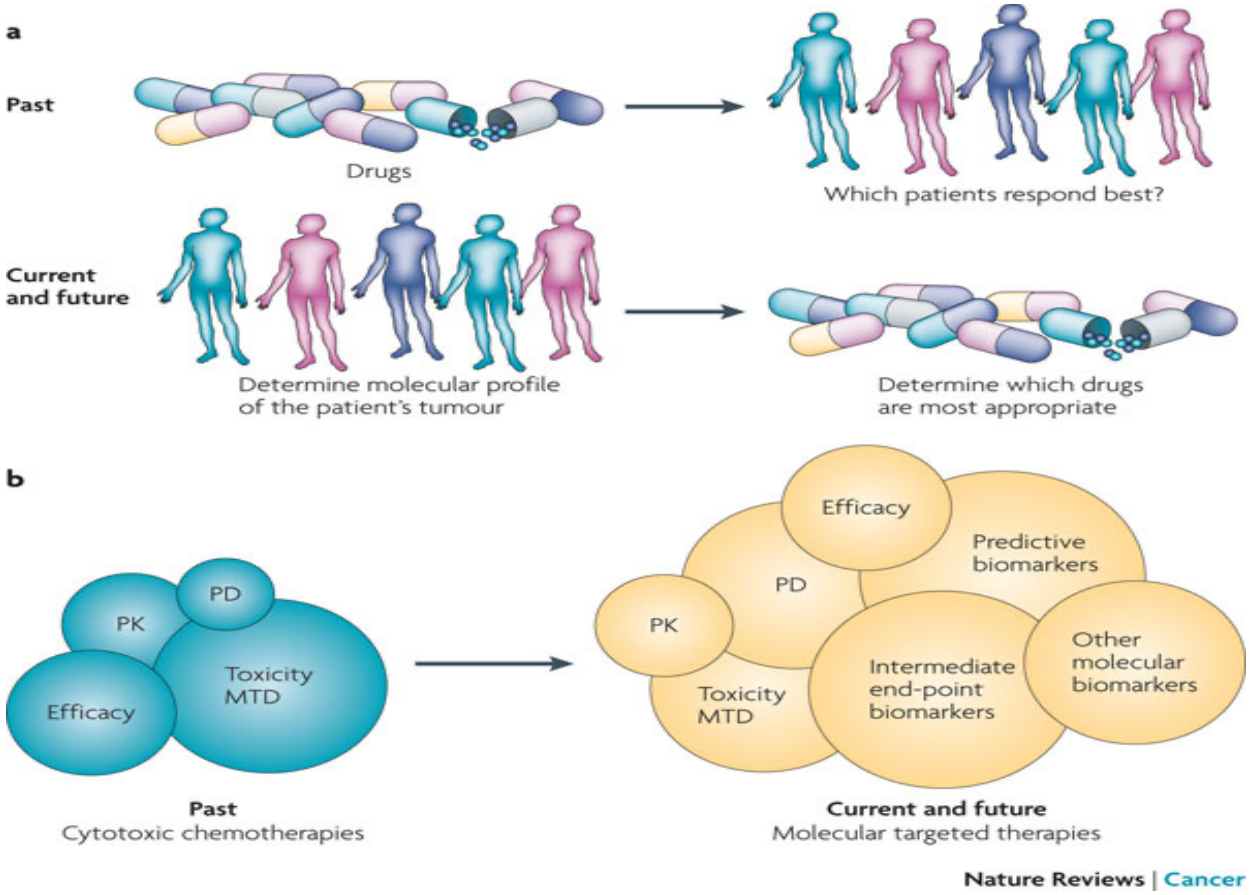
ISLB
INTERNATIONAL SOCIETY OF LIQUID BIOPSY

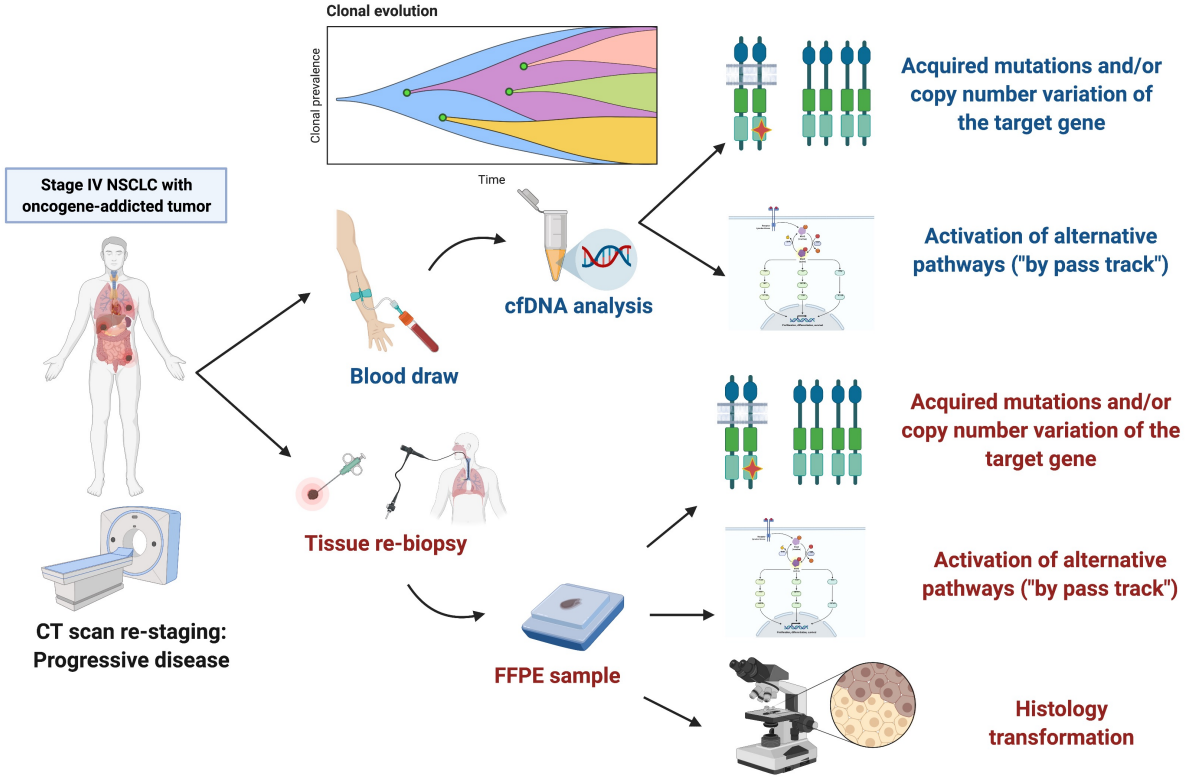
Center for Thoracic Oncology

Mount Sinai
The Tisch Cancer Institute

Current Treatment and Trial Paradigm



Clinical utility of tissue and liquid biopsy in oncogene-addicted NSCLC



Main liquid biopsy techniques used

NGS-based approaches:
- ✓High sensitivity
- ✓Multiplex
- ✓Gene rearrangements
- ✓Gene amplifications

PCR-based approaches:
- ✓Variable sensitivity
- ✓Single gene testing
- ✓Only for mutations

Main techniques used for tumor tissue

NGS-based approaches:
- ✓High sensitivity
- ✓Multiplex
- ✓Gene rearrangements
- ✓Gene amplifications

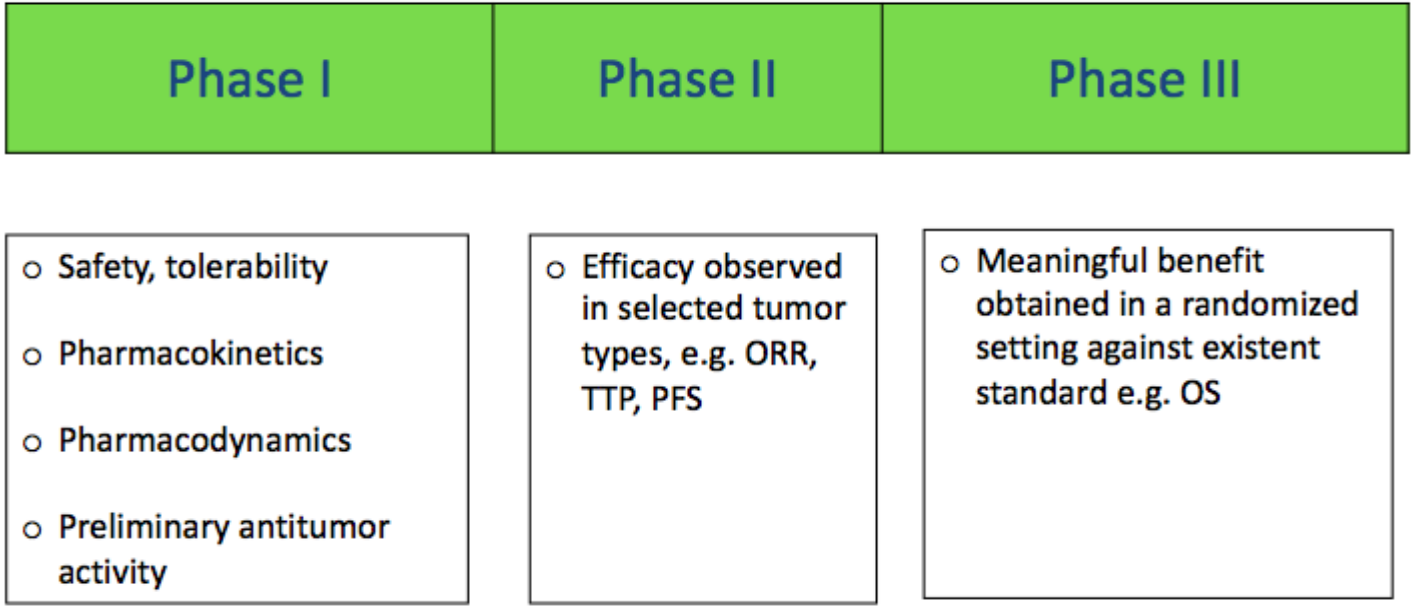
FISH:
- ✓Gene rearrangements & amplifications

PCR-based approaches:
- ✓Variable sensitivity
- ✓Single/Multiplex gene testing
- ✓Only for mutations

IHC:
- ✓Protein expression

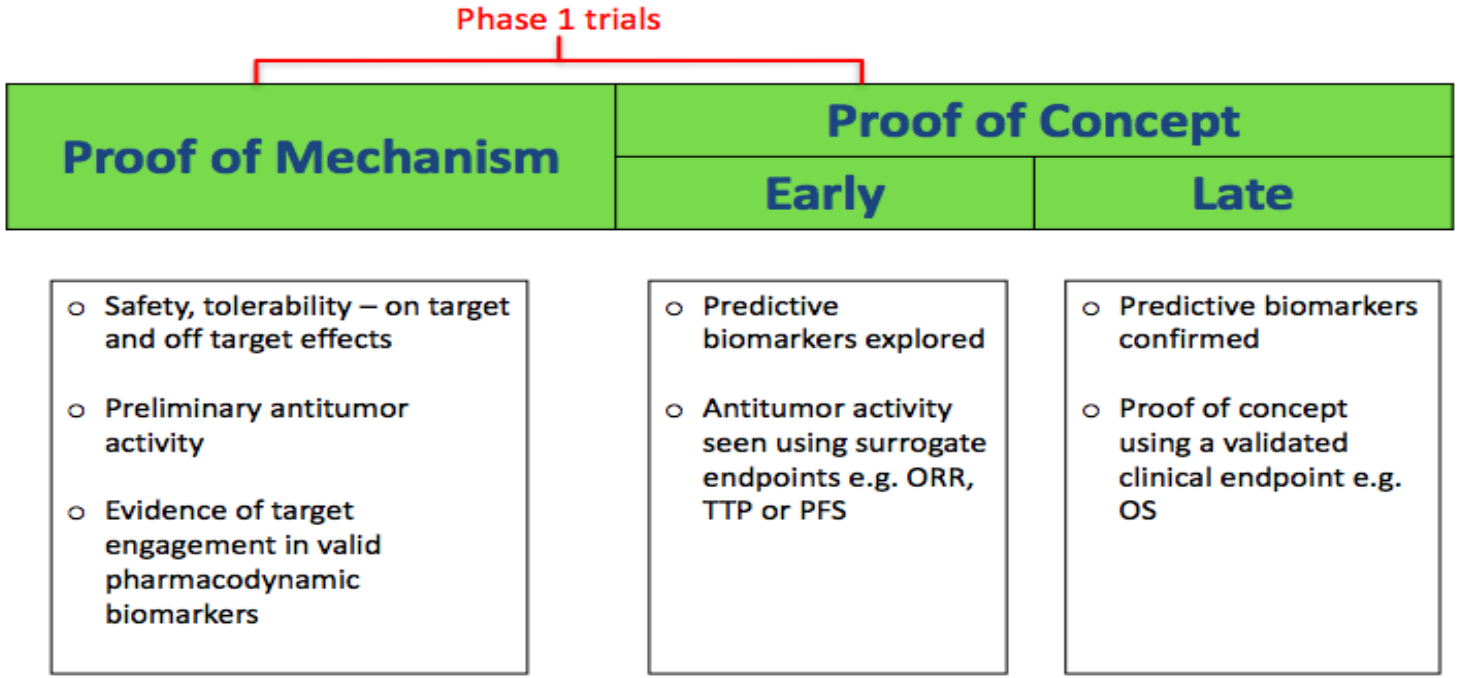
Rolfo C, et al. J Thorac Oncol 2021

The Traditional Drug Development Paradigm



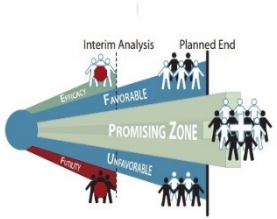
Courtesy of David Hong

The Current Drug Development Paradigm



Courtesy of David Hong

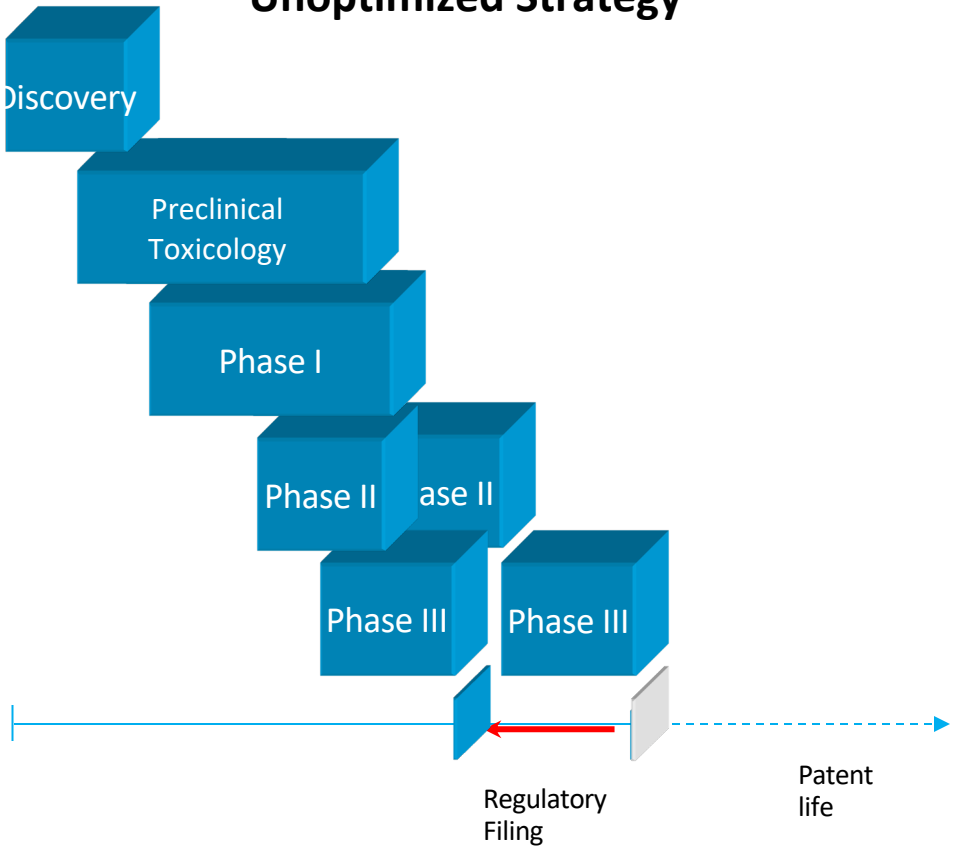
Selected new designs in drug development



Genotype driven	**Basket trials**	Test the effect of one or more drugs on one or more single mutation in a variety of cancer types
	Umbrella	Test the impact of different drugs in different mutations in a single type of cancer
New designs	**Adaptative trial**	based on modifying parameters of a clinical trial evaluating a treatment according to outcomes in participants
	N of 1	Assessing the administration of an investigational agent over a short period of time
	Windows of opportunity	Assessing the administration of an investigational agent over a short period of time

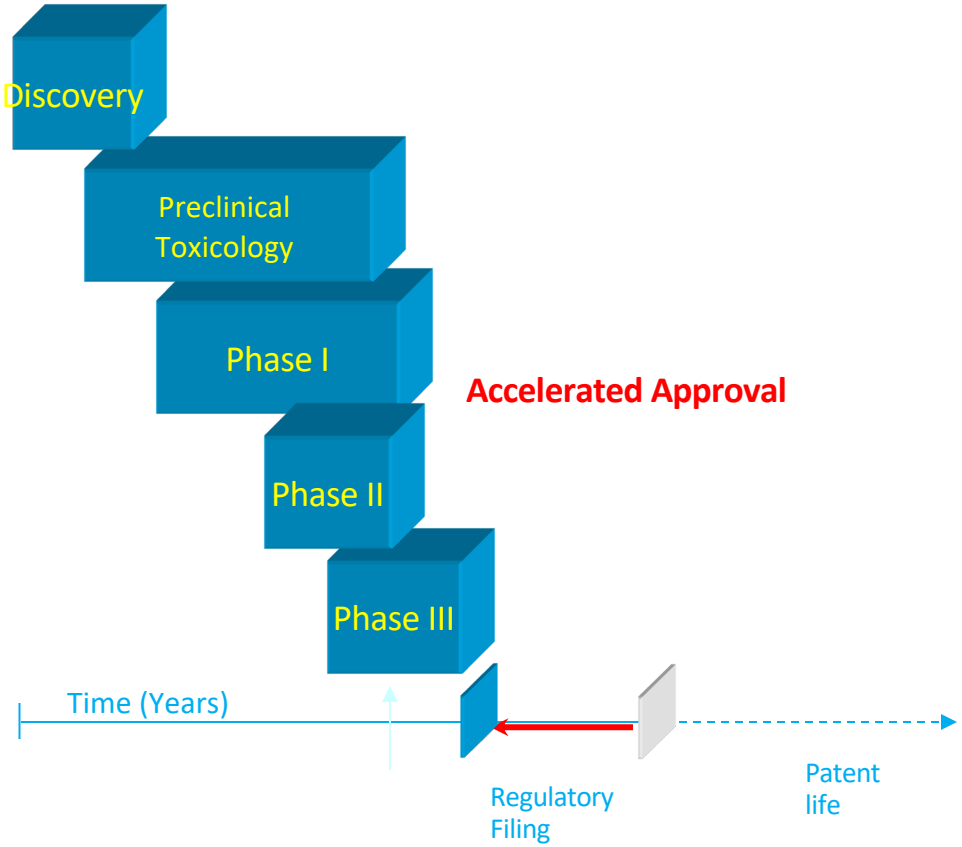
Efficiency Gain From A Thoughtful Scientific/Regulatory Strategy

Unoptimized Strategy

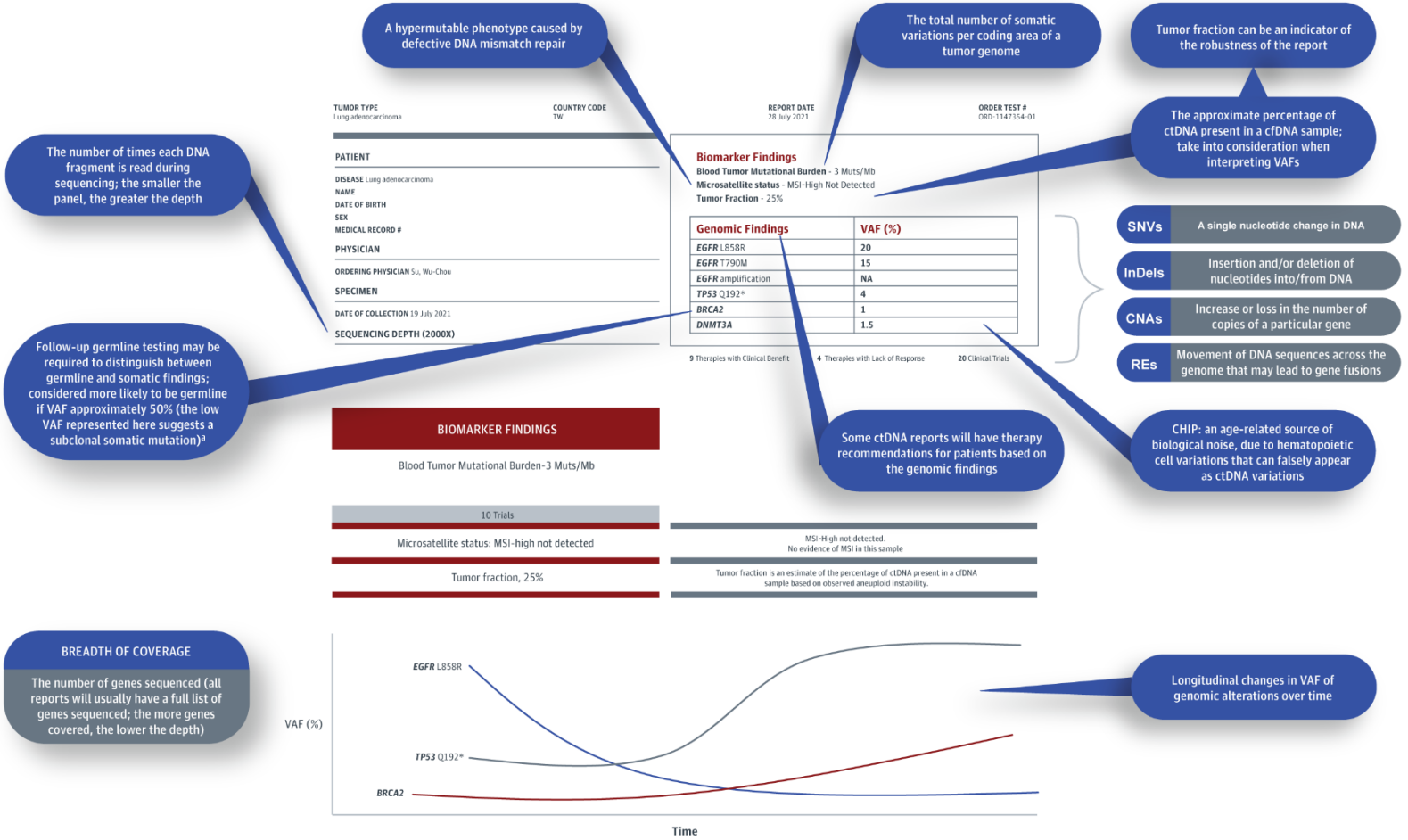


Adapted from Postel-Vinay *et al.* , Annals of Oncol. 2016

Efficiency Gain From A Thoughtful Scientific/Regulatory Strategy

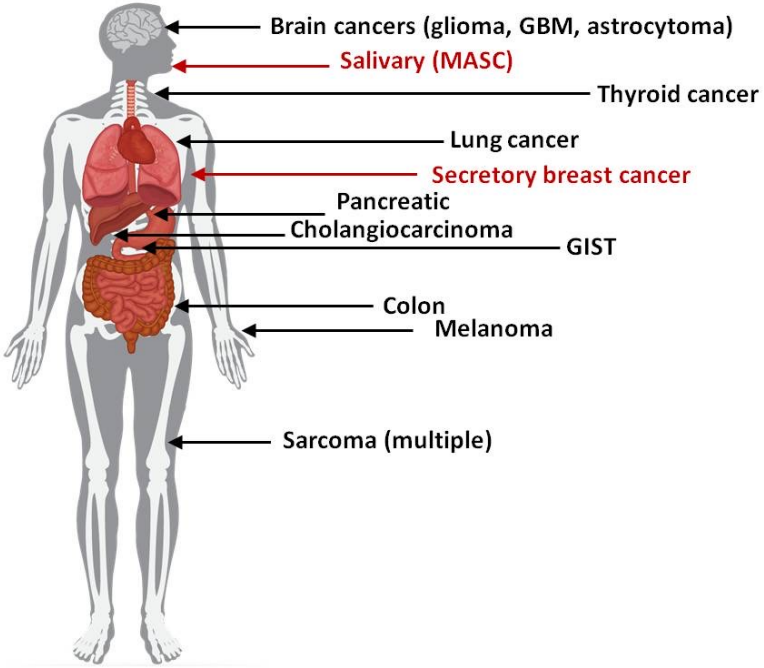


Adapted from Postel-Vinay *et al.* , Annals of Oncol. 2016

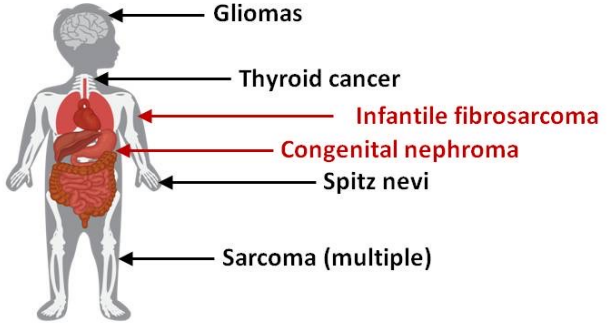


Krebs et al (Rolfo), JAMA Oncology OCT 2022

TRK fusions found in diverse cancer histologies



- Common cancer with low TRK fusion frequency
- Rare cancer with high TRK fusion frequency

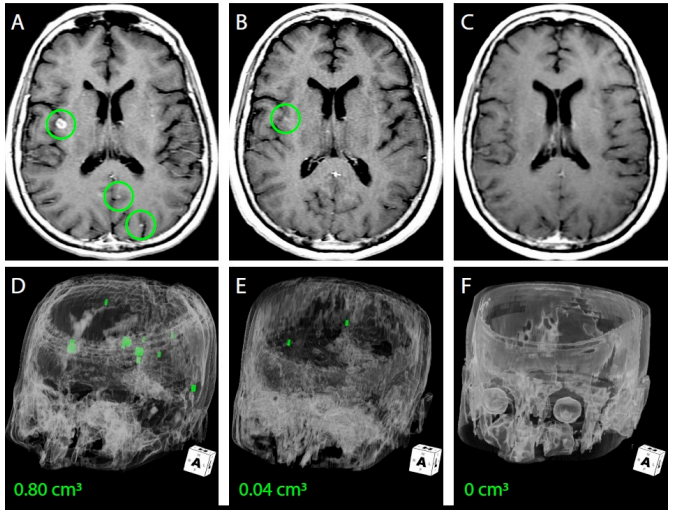


Estimated 1,500–5,000 patients harbor TRK fusion-positive cancers in the United States annually

Presented By David Hyman at 2017 ASCO Annual Meeting

TRK Inhibitors Are Active in Brain Metastases

Patients With Brain Metastases	Larotrectinib[1]	Entrectinib[2]
ORR (at all sites), %	60% (n = 5)	50% (n = 12)
Intracranial ORR, %	66% (n = 3)	55% (n = 11)
Intracranial PFS, mo	Not reported	14.3



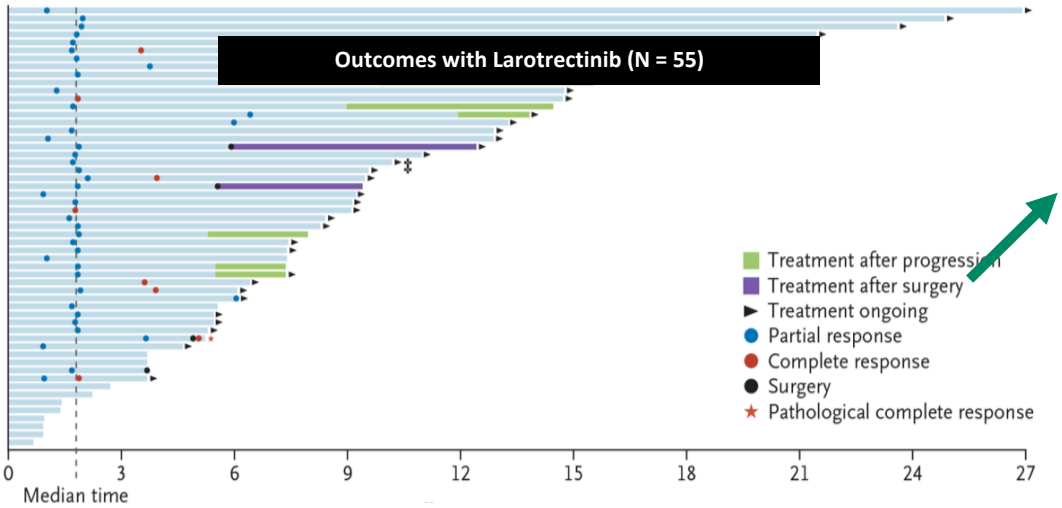
***TRK* Fusion–Positive Lung Cancer With Brain Metastases Treated With Larotrectinib[3]**

- Confirmed PR (-34%)
- Near intracranial CR (-95%, volumetric)
- Remains on therapy at 6+ mo

1. Drilon. ASCO 2019. Abstr 2006. 2. Doebele. Lancet Oncol. 2020;21:271. 3. Rosen. JCO Precis Oncol. 2019;3:PO.19.00009.

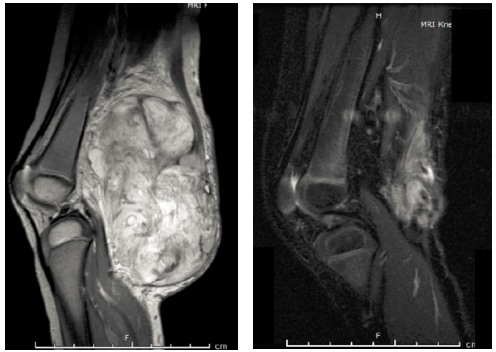
Slide credit: clinicaloptions.com

Larotrectinib Trial Demonstrates Potential for Neoadjuvant Targeted Therapy in *TRK*+ Cancers



Median time to response: 1.8 mo

Treatment Duration, mo



Baseline | Cycle 3

2 year-old requiring leg amputation for TRK fusion-positive sarcoma
- dramatic response to larotrectinib
- underwent limb-sparing surgery with no functional deficits
- pathologic complete response

2-Yr-Old Requiring Leg Amputation for *TRK* Fusion–Positive Sarcoma

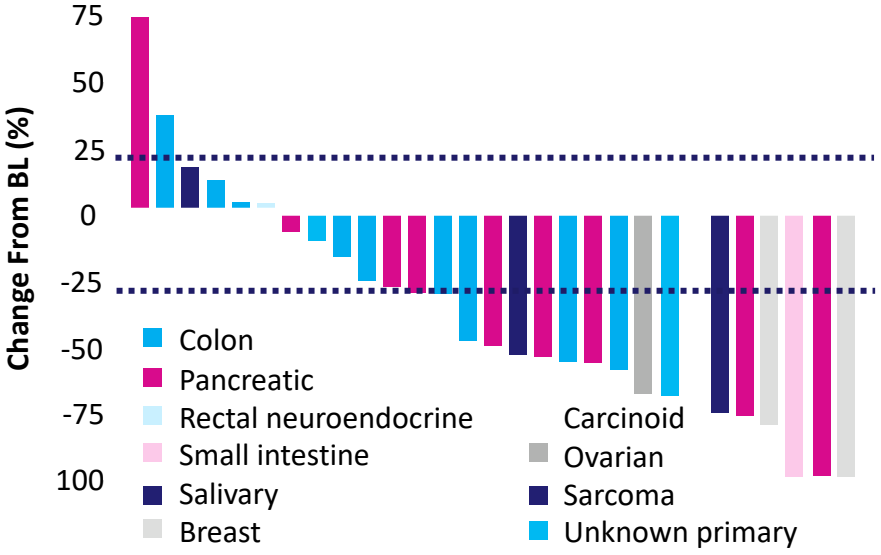
- Dramatic response to larotrectinib
- Limb-sparing surgery conducted with no functional deficits
- pCR achieved

Drilon. N Engl J Med. 2018;378:731. Kummar. Target Oncol. 2018;13:545.

Slide credit: clinicaloptions.com

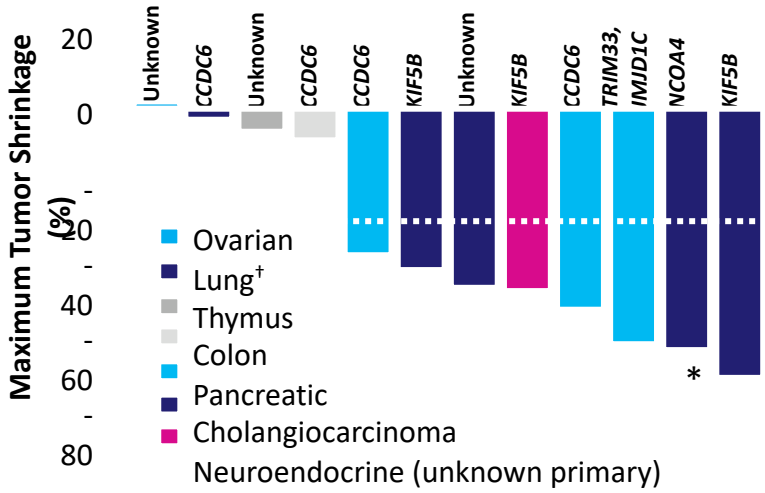
RET Inhibitors Are Active in Fusion-Positive Cancers

Tumor Response by Tumor Type: Selpercatinib (n = 32)



- N = 32 response evaluable patients
  - ORR (95% CI): 47 (29-65)

Tumor Response by *RET* Fusion Partner in Various Tumor Types: Pralsetinib (n = 12)



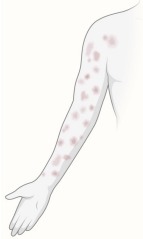
*Pt received alternate starting dose during dose escalation; transitioned to 400 mg QD. †Included mixed sarcoma/adenocarcinoma, mixed SCLC/NSCLC, atypical carcinoid.

- n = 12 response evaluable patients
  - ORR (95% CI): 50 (21-79); responses observed in all pts with pancreatic adenocarcinoma (n = 3) and cholangiocarcinoma (n = 2)

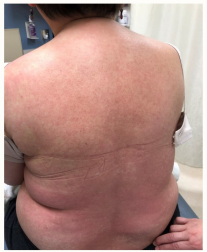
Subbiah. ASCO 2020. Abstr 109. Subbiah. AACR 2021. Abstr CT011.

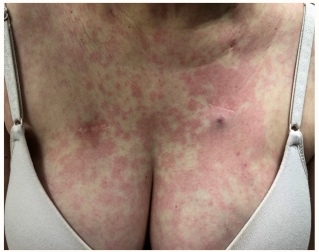
Slide credit: clinicaloptions.com

Hypersensitivity Reactions to Selpercatinib Treatment with Prior Immune Checkpoint Inhibitor Therapy

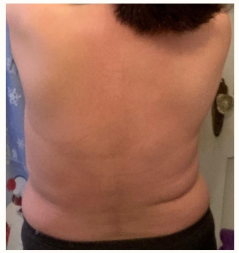


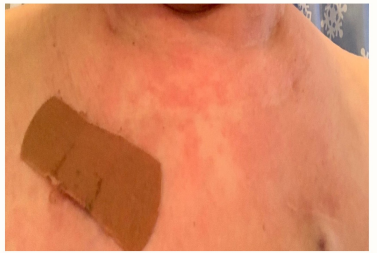
Diffuse grade 3 skin rash



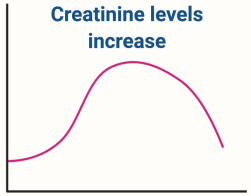


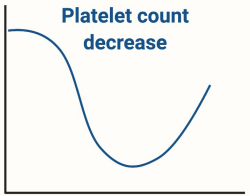
Rapid improvement after <24h oral low-dose steroids





Lab results alterations



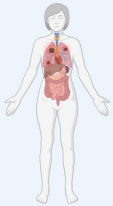


Grade 2 diarrhea with stool culture negative

Body temperature: Grade 1 fever (37.4°C)

Punch skin biopsy revealed spongiotic dermatitis, superficial perivascular lymphocytic infiltrate, rare eosinophils, and pigment incontinence that favored drug reaction

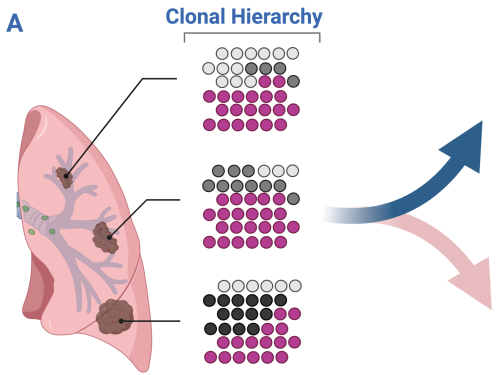
- 52-yr Caucasian, female, never smoker
- Lung adenocarcinoma, Stage IV
- *KIF5B-RET* fusion
- Selpercatinib as 4th line, after progressing on carboplatin/pemetrexed, nivolumab, and cabozantinib
-On C1D8 the patient presented with grade 2 diarrhea, grade 1 fever for 2 days, and grade 3 diffuse cutaneous rash. Labs revealed thrombocytopenia and creatinine increase



McCoach & Rolfo, et al. JTO Feb 2022

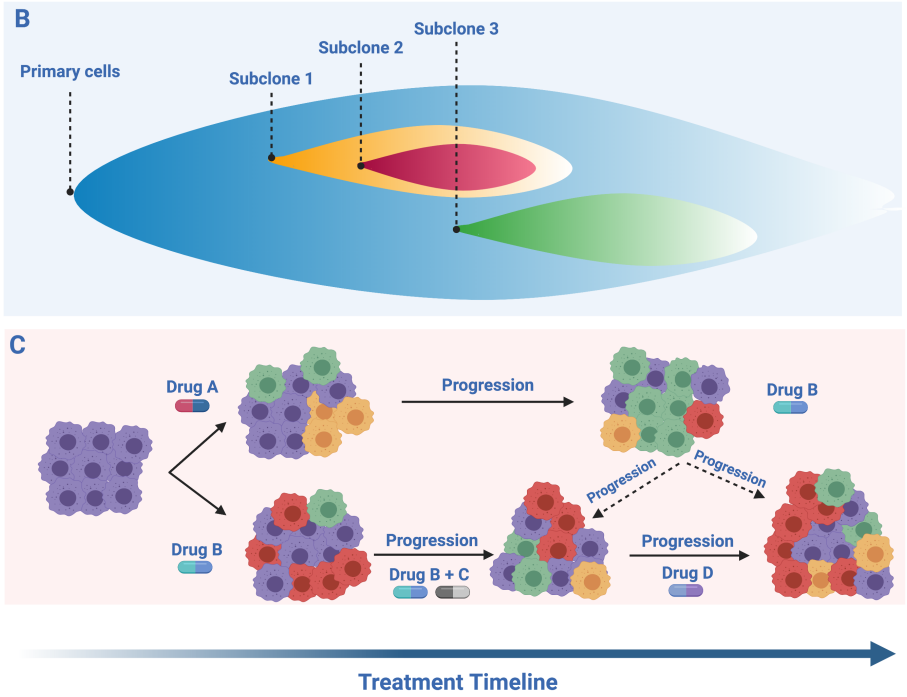
Acquired resistance is a dynamic process

Mechanisms of acquired resistance might be heterogenous and multiple mechanisms can simultaneously occur in the same patient, reflecting the clonal heterogeneity of the tumor



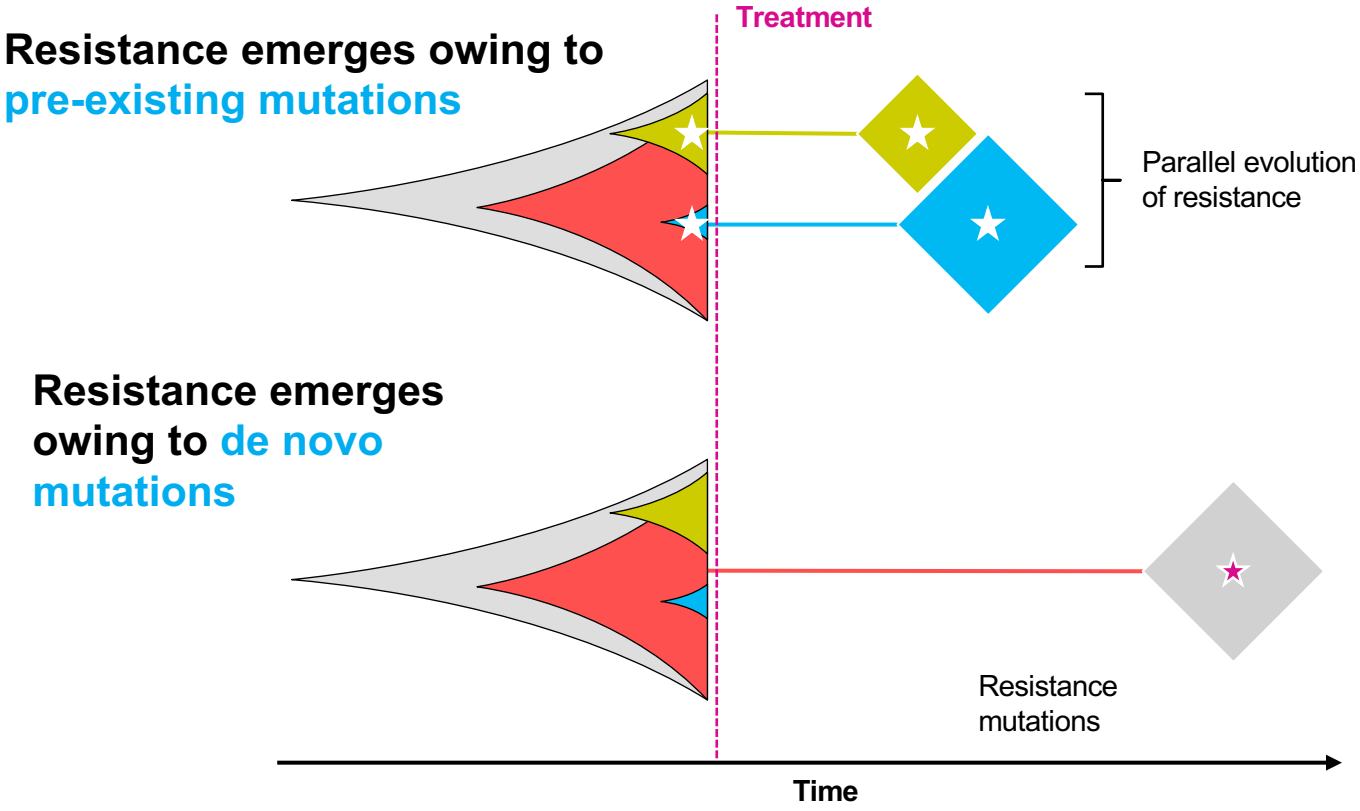
Tracking the clonal evolution of the tumor over time might allow the implementation of tailored therapeutic approaches

The clonal evolution of the tumor under the selective pressure of anticancer therapies



Passaro A, et al. (Rolfo) ESMO Open 2020

Clonal evolution of treatment resistance

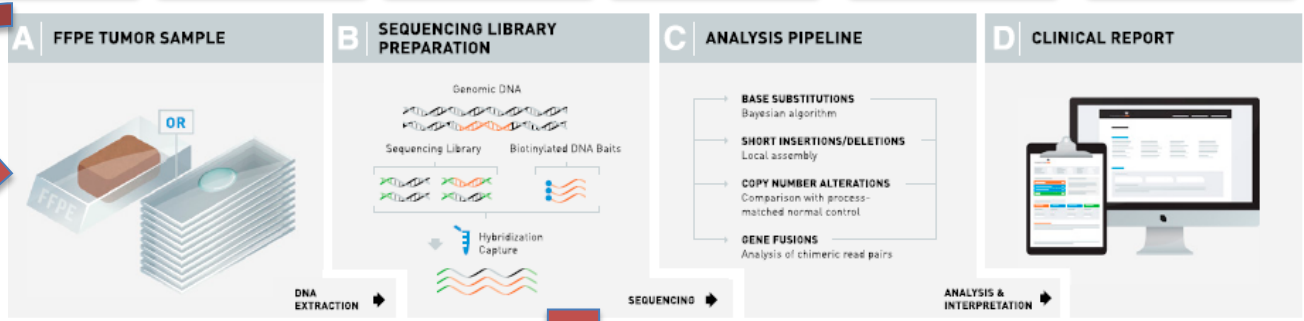


Our New Way to Work . . . Molecular Tumor Board

Patient case is derived from his doctor

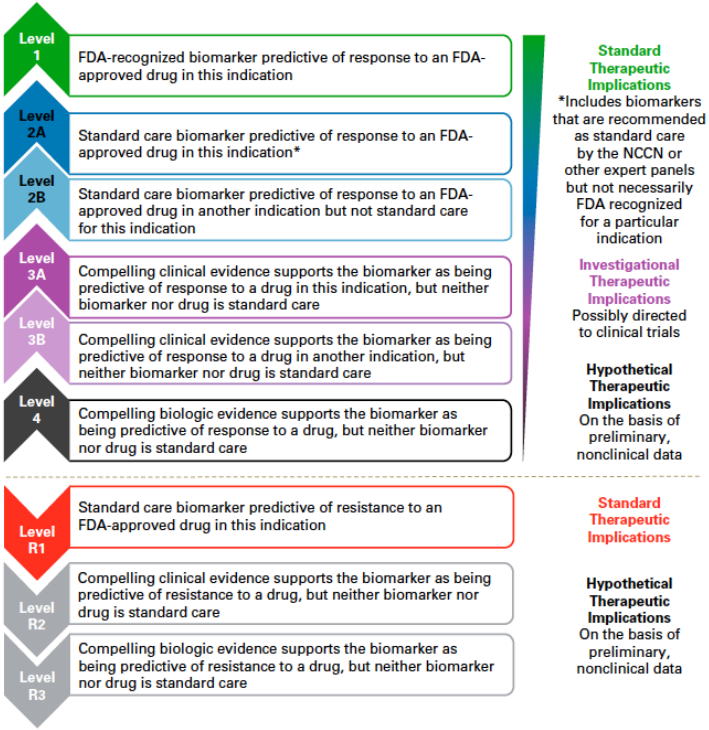
Molecular Tumor Board

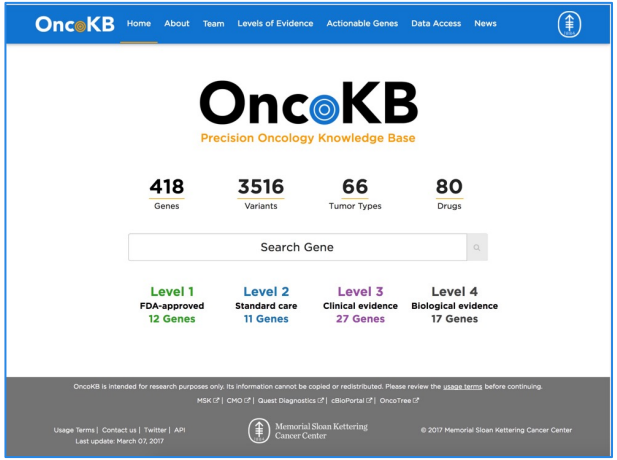
Oncologist | Mol. Pathol | Gyneco | Thorax | Geneticist | Nav. nurse



Molecular Tumor Board → **Report with therapeutic proposal** → Referral Doctor Discussion

Levels of evidence tools have been developed to rank genomic alterations: OncoKB





Summary

418 genes fully annotated

3516 functionally significant SNVs

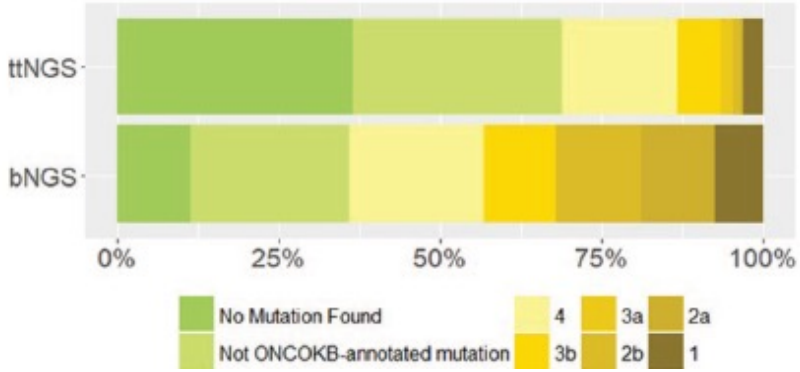
80 drugs associated with a OncoKB Level of Evidence

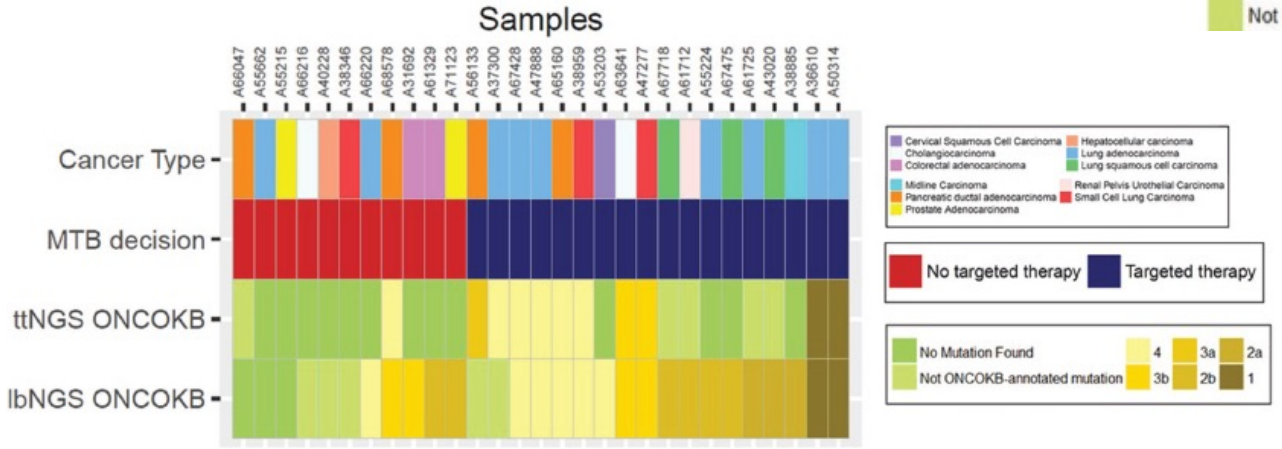
OncoKB annotation incorporated into MSK-IMPACT reports

~1,000 reports / month

Chakravarty D, et al. JCO Precis Oncol 2017;

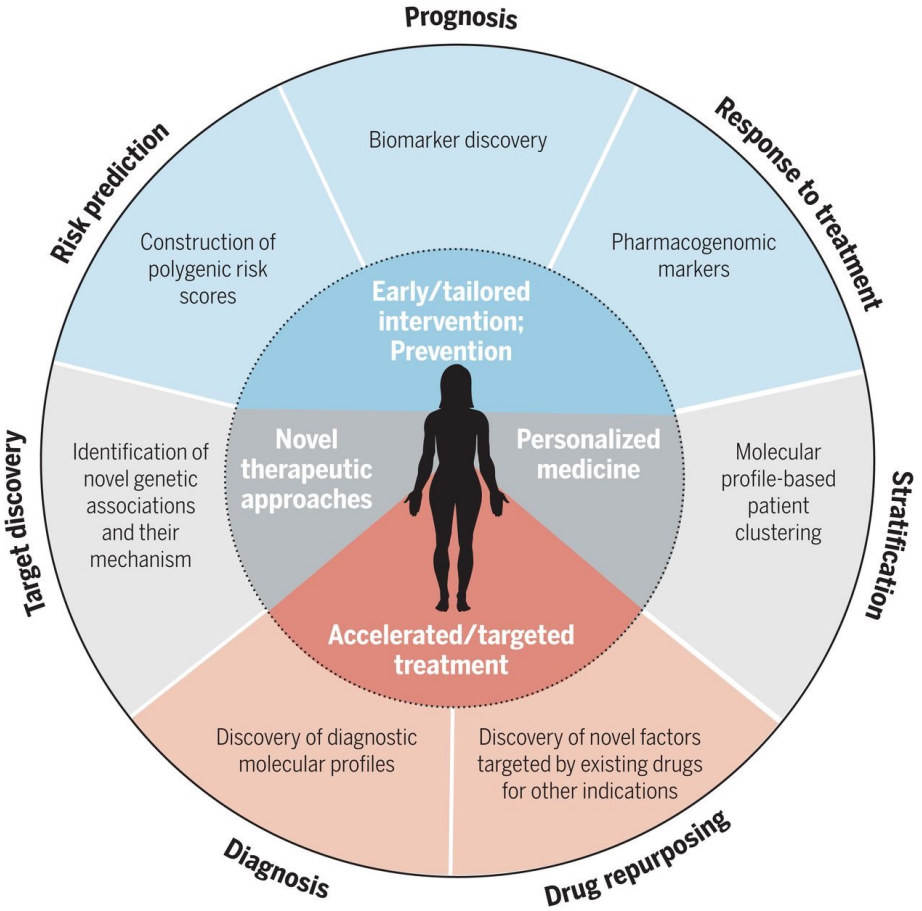
Multidisciplinary molecular tumour board: a tool to improve clinical practice and selection accrual for clinical trials in patients with cancer





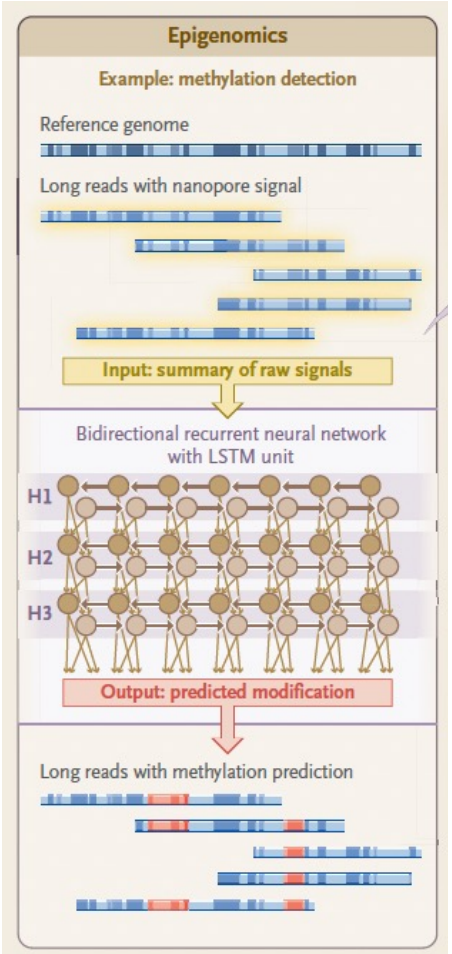
Rolfo C, et al. ESMO Open 2018

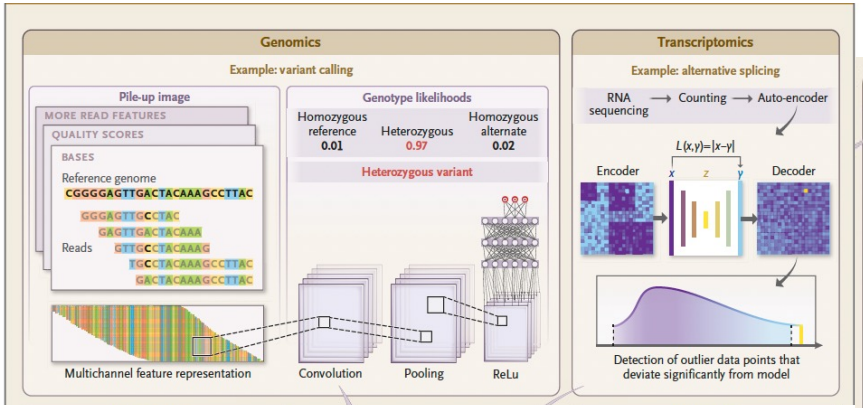
Attributes of a Successful Precision Medicine Program

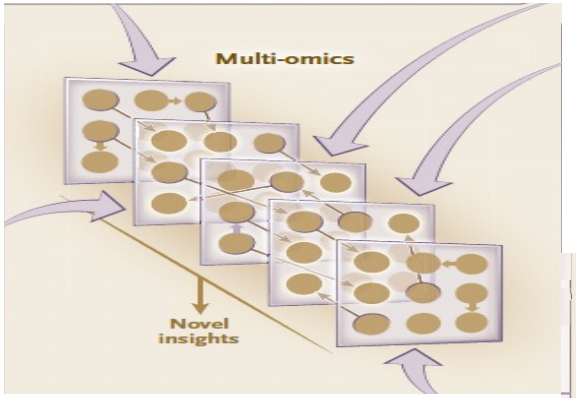


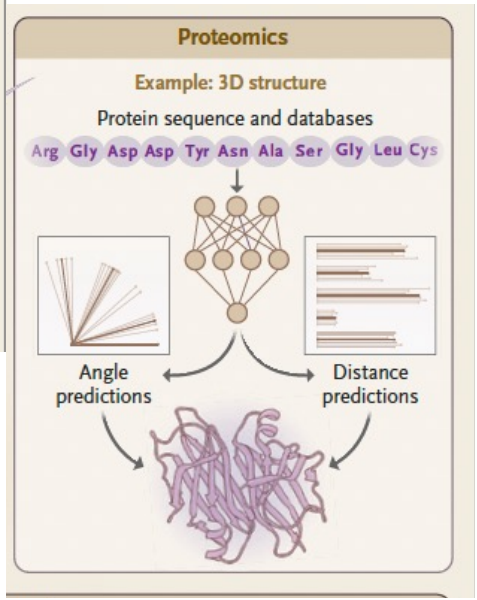
Zeggini et al, *Science* 27 Sep 2019:

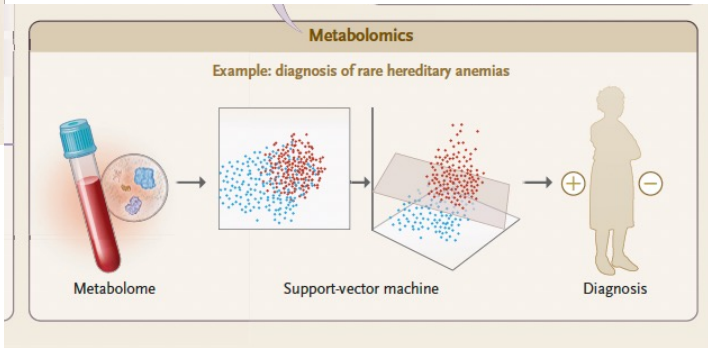
J. Ersek et al, *American Society of Clinical Oncology Educational Book* 38188-196.







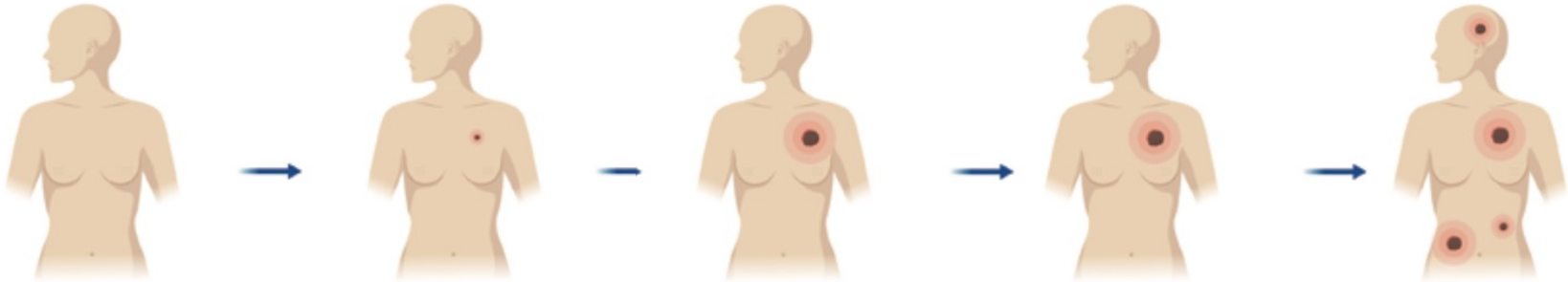




Gomes et al, NEJM 388;26 June 29, 2023

Liquid vs. tissue biopsies in cancer interception

Model 1 for cancer interception (Avoiding cancer)	Model 2 for mestasis interception (Avoiding dissemination: metastasis interception)			



Predisposition	Early diagnosis	Late detection	Monitoring	Dissemination
Liquid biopsy	Liquid biopsy	Tissue biopsy	Liquid biopsy	Tissue biopsy

Cancer interception

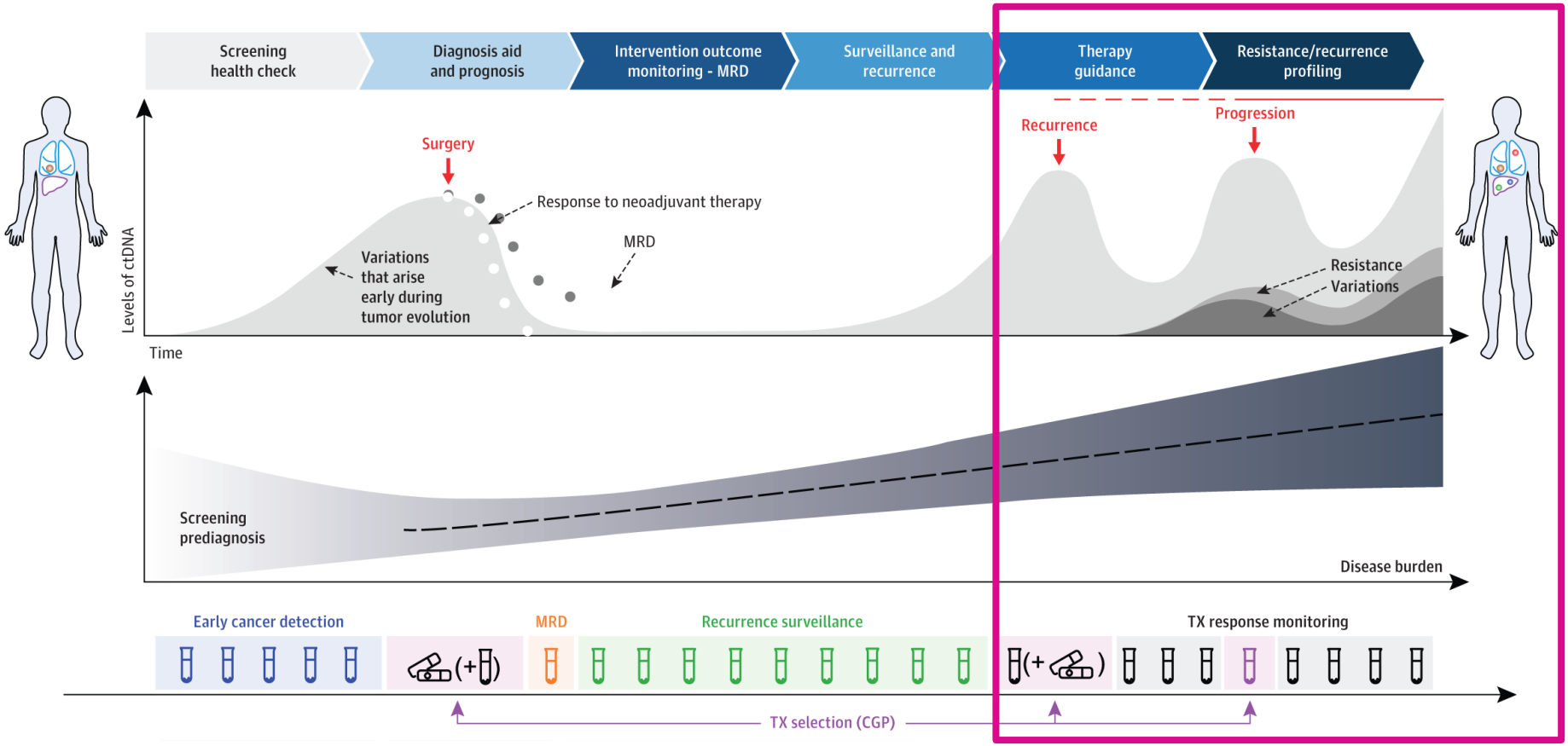
Survival rates

Mj. Serrano, Critofanilli et al (Rolfo) Cancer Discov 2020;10:1635–44

Challenges to implementation of genomic medicine

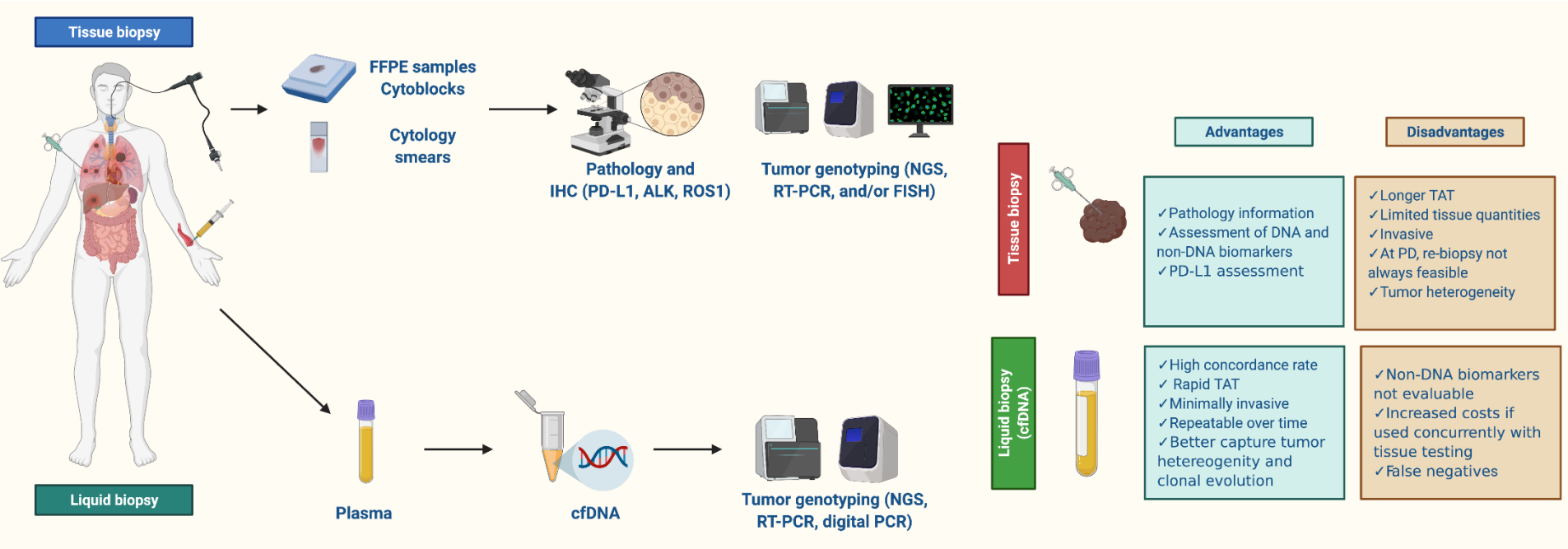
- Lack of familiarity and understanding by patients and clinicians
- Poor access to genomic medicine expertise and testing
- High cost and lack of reimbursement for genetic or genomic tests and services
- Potentially overwhelming and rapidly evolving nature of genomic information
- Need for extensive informatics and infrastructure to integrate genomic results into electronic medical records
- Non-acceptance of genomic medicine by institutions and clinicians
- Potential burden of following up genotyped patients when the clinical significance of genomic variants changes or becomes clear

From Manolio et al, Lancet. 2019 Aug 10;394(10197):511-520

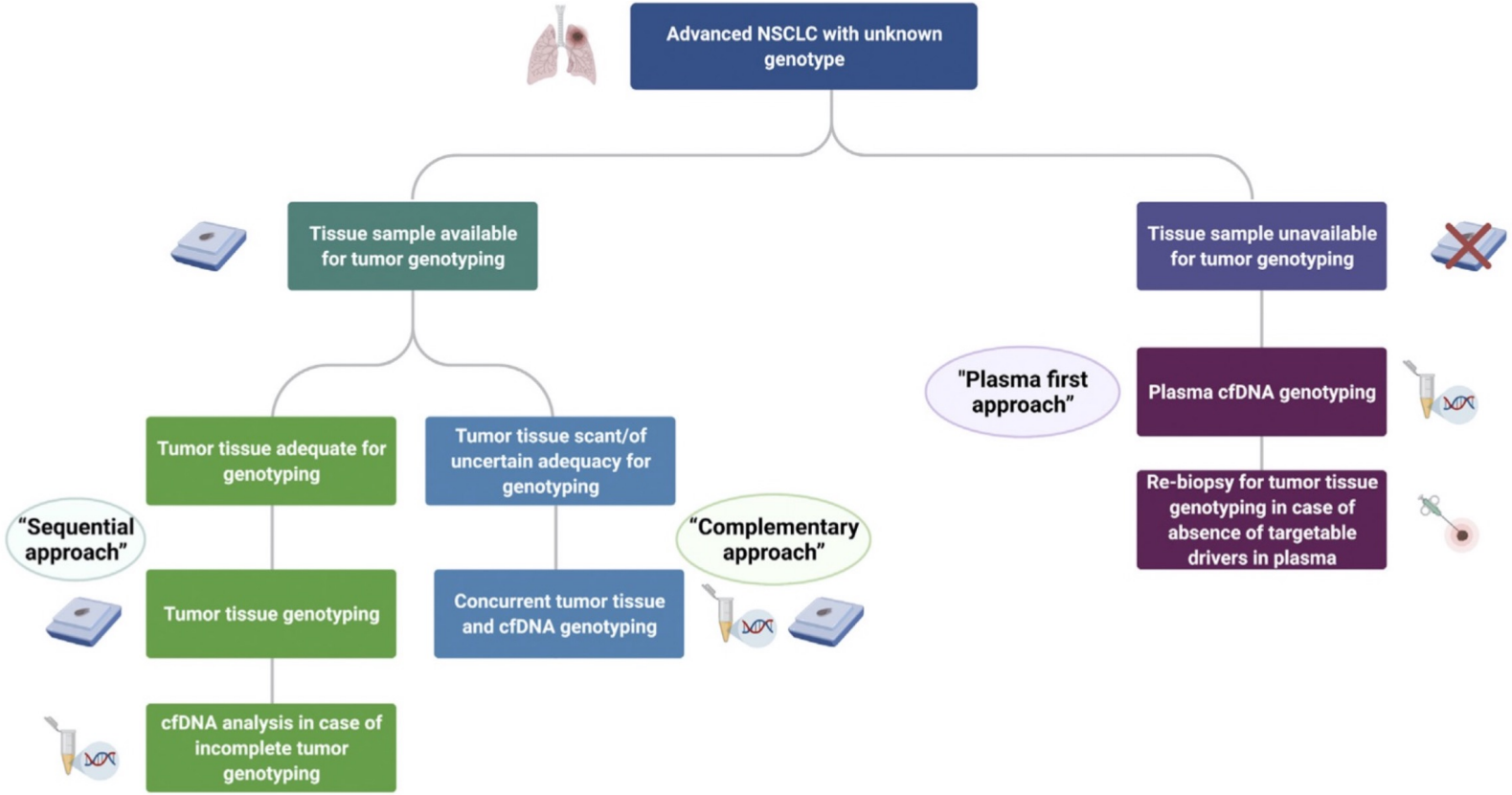


Krebs et al (Rolfo), JAMA Oncology OCT 2022

Tissue vs. Liquid biopsy



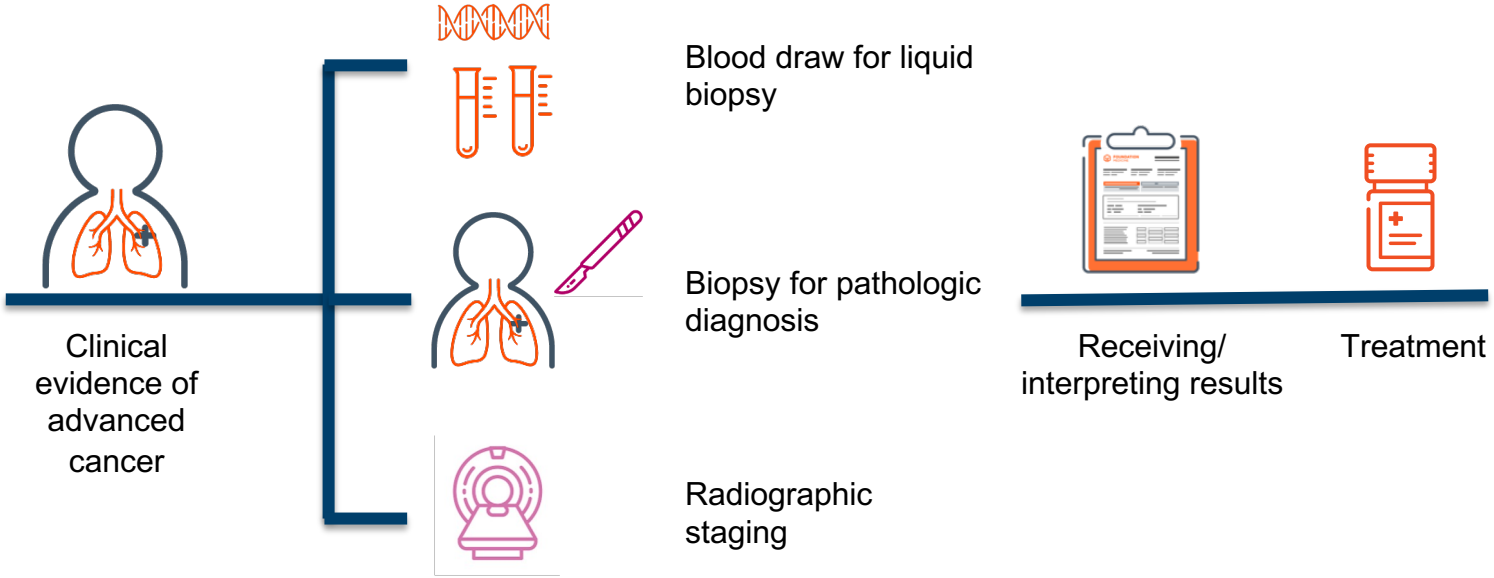
Rolfo C, *et al. J Thorac Oncol* 2021;16(10):1647-1662.



Rolfo C, et al. J Thorac Oncol 2021

Expedited diagnostic odyssey

Stacking diagnostic steps may be able to shorten the diagnostic odyssey



Rolfo et al, in preparation

Tailoring treatment with Liquid Biopsy

Osimertinib start with an intracranial CR and extracranial PR

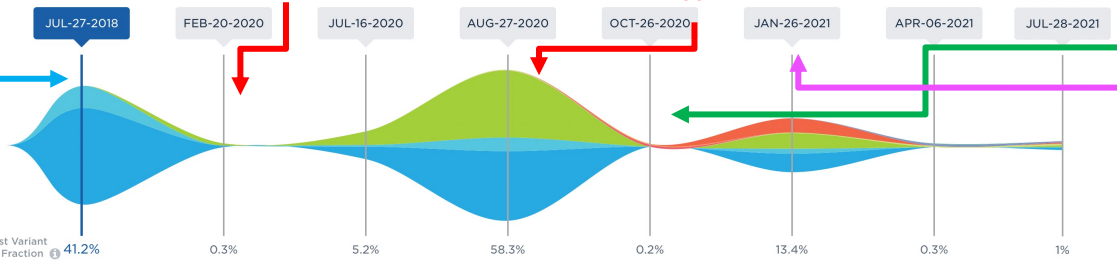
52-year-old never smoker female; diagnosed in July 2018 with cT4 N3 M1c lung adenocarcinoma (stage IVB).

After 18 mos oligo-PD (LN mets) → SBRT and continued osi

Further disease progression → osimertinib stopped; switch to erlotinib

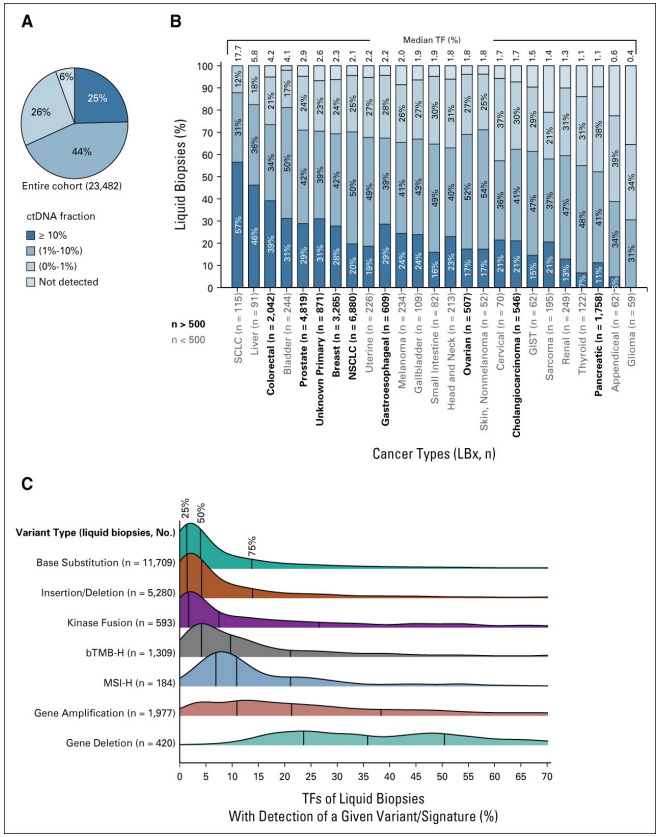
PET/CT in Nov. 2020: CR

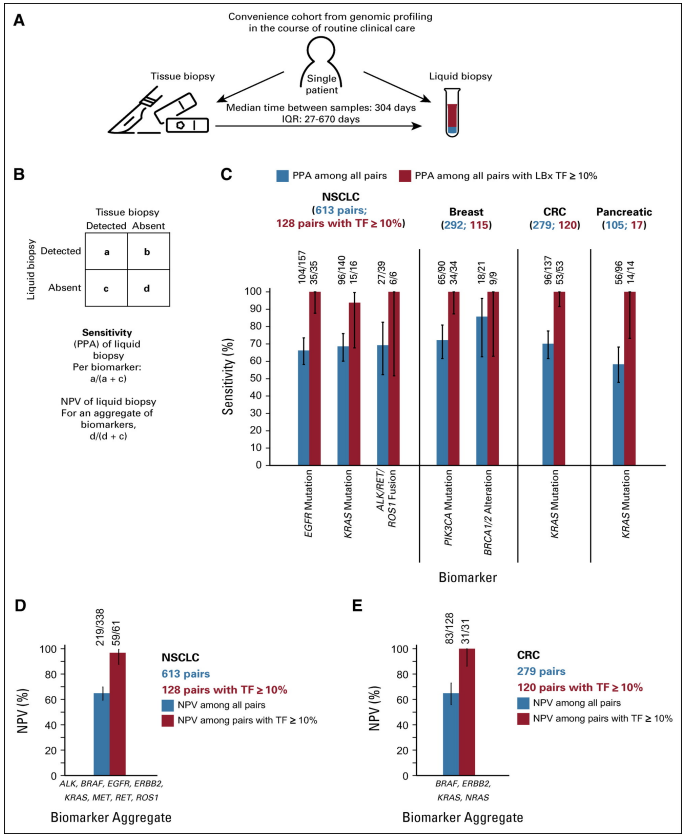
Erlotinib discontinuation → platinum-based chemo start



Genetic Alteration	% cfDNA or amplification							
EGFR E746_A750del	41.2%	0.2%	4.7%	58.3%	ND	13.4%	ND	1%
EGFR C797S	ND	0.3%	5.2%	55.6%	ND	10.7%	ND	0.7%
ARID1A Q456Q	ND	ND	ND	0.2%	ND	0.2%	0.3%	0.6%
EGFR T790M	ND	ND	ND	ND	ND	9.6%	ND	0.4%
TP53 C275Y	ND	ND	ND	ND	ND	ND	0.1%	0.2%
ARID1A F1728F	ND	ND	ND	ND	ND	ND	0.3%	0.2%
TP53 S127F	6.5%	ND	0.4%	7.6%	ND	2.6%	ND	0.2%
***BRAF* Amplification**	2.2%	ND	ND	ND	ND	ND	ND	ND
***CDK6* Amplification**	2.2%	ND	ND	ND	ND	ND	ND	ND
***EGFR* Amplification**	3.4%	ND	ND	4.2%	ND	ND	ND	ND
***NTRK2* L699L**	-	-	-	-	0.2%	ND	ND	-
***EGFR* N338N**	ND	ND	ND	ND	0.1%	ND	ND	ND
***FGFR1* V795I**	ND	ND	ND	ND	ND	ND	0.1%	ND

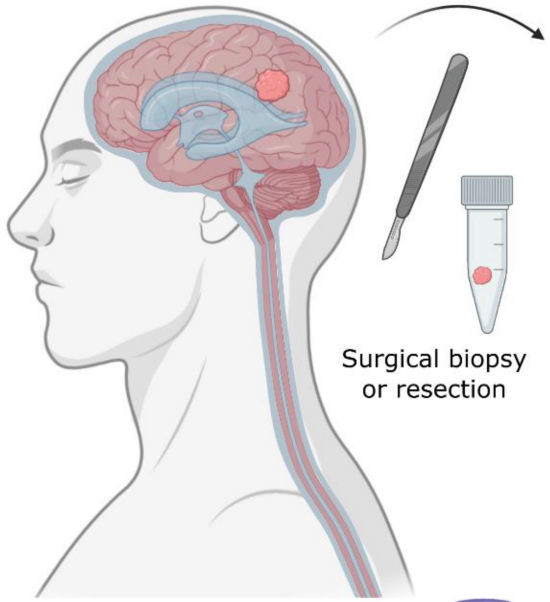
Tumor Fraction Correlates With Detection of Actionable Variants Across > 23,000 Circulating Tumor DNA Samples





- Elevated ctDNA shed is associated with both high sensitivity and negative predictive value for detection of actionable Genomic Alterations .
- The presence of elevated TF suggests adequate tumor profiling and may reduce the value of subsequent reflex to confirmatory tissue testing in patients with negative LBx results.

Husain at al, JCO PO, OCT 2022



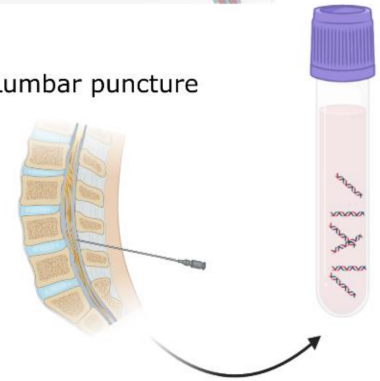
Surgical biopsy or resection

Solid biopsy (tumour specimen)

Advantages
Allow histological diagnosis

Limitations
Very invasive and risky procedure
Sometimes not feasible due to tumour anatomical location
Not representative of tumour heterogeneity
Static snapshot

Lumbar puncture



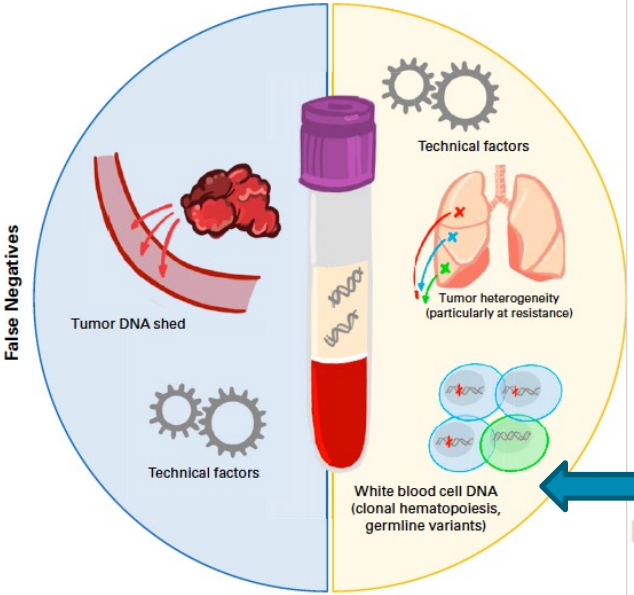
Liquid biopsy (CSF ctDNA)

Advantages
Less-invasive and easier to obtain than a tumour biopsy
CSF obtained as SOC for some patients
Concordance with tissue characterisation
Representative of intratumour and interlesion heterogeneity
Longitudinal real-time monitoring

Limitations
No histological characterisation
Lack of standardisation
Contraindications for lumbar puncture
Limited sensitivity

Escudero et al, Cancers **2021**, *13*(9), 1989

Sources of false positive and false-negative results in plasma NGS

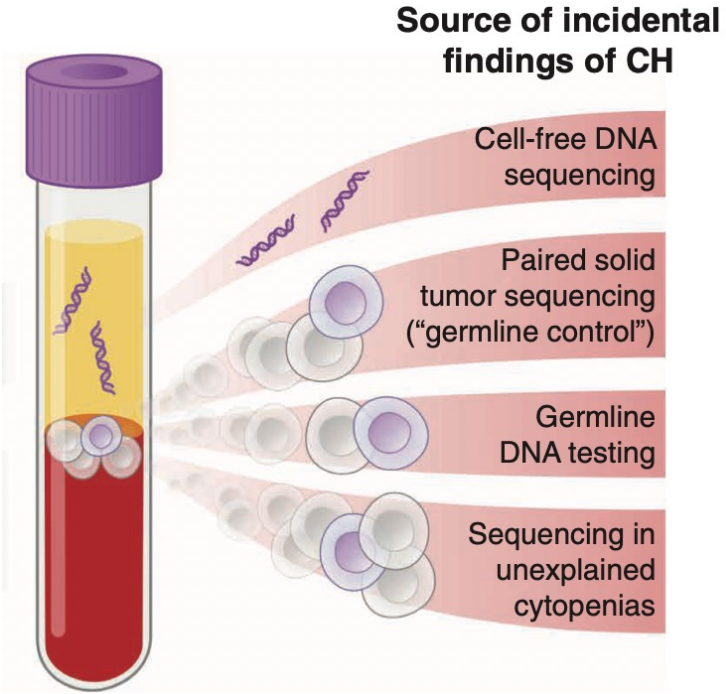


"False Positives"
in Liquid Biopsy

Technical Factors:
Sample differences
(> 6 months from tissue to plasma sampling)

WBC contamination:
Germline Variants
Clonal Hematopoiesis

Tumor Heterogeneity:
Positive Plasma & Negative Tissue
(assumes tissue is "Gold standard")

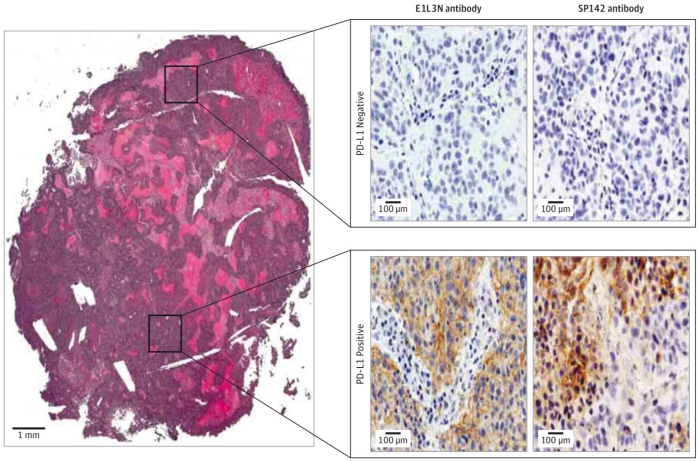


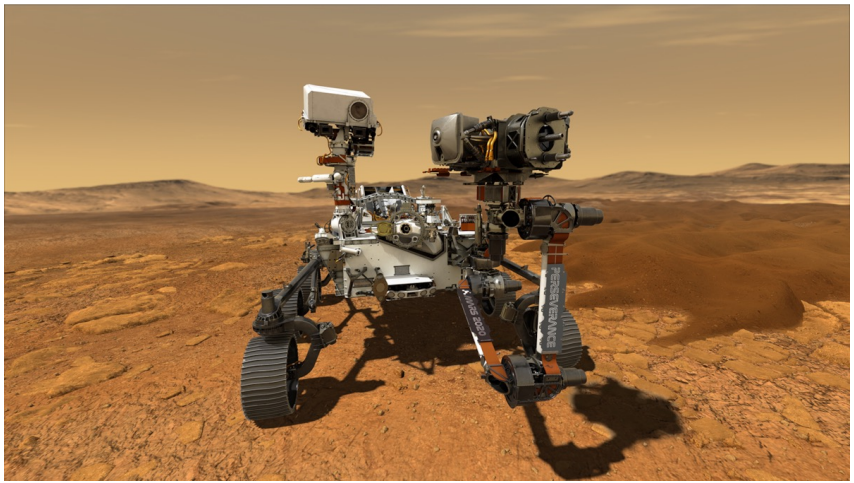
Paweletz CP, et al. JCO Precis Oncol 2019

Köhnke – Cancer Discov 2021

Heterogeneity of PD-L1 Expression

An imperfect but useful biomarker

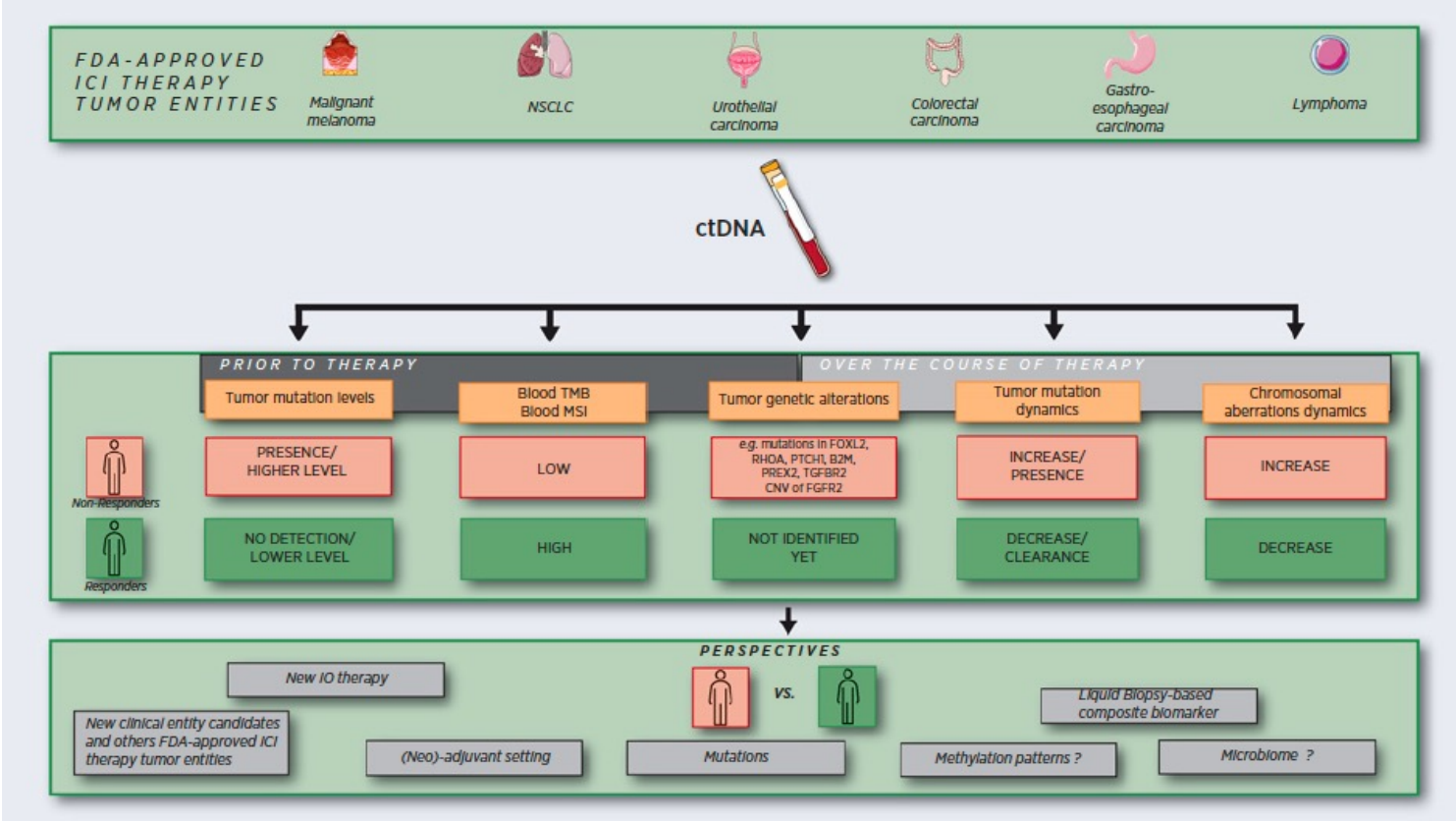




- **Intratumor** heterogeneity
- **Intrapatient** heterogeneity

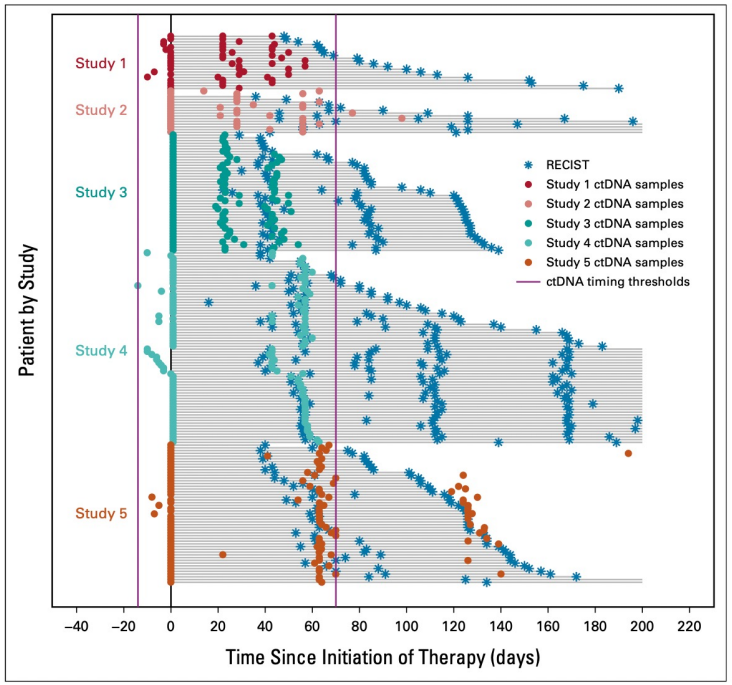
McLaughlin et al, JAMA Oncol. 2016;2(1):46-54

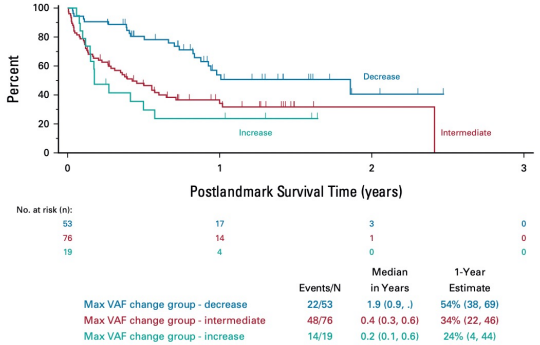
Use of Liquid Biopsy in Immunotherapy

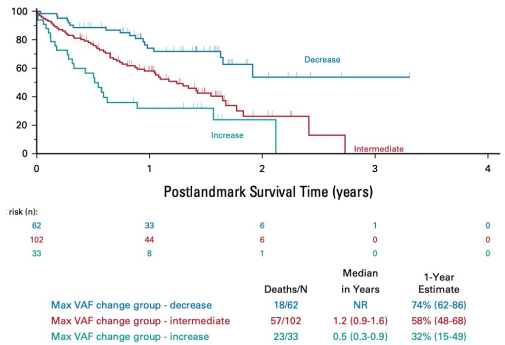


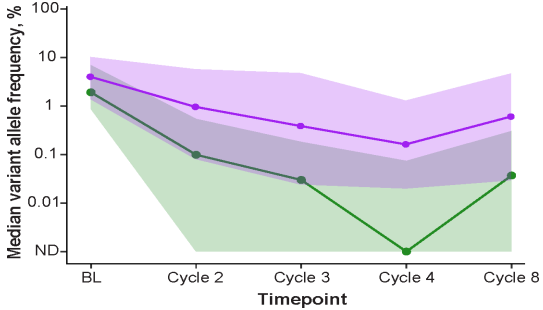
Stadler J, et al. Cancer Res 2022

Changes in Circulating Tumor DNA Reflect Clinical Benefit Across Multiple Studies of Patients With Non–Small-Cell Lung Cancer Treated With Immune Checkpoint Inhibitors









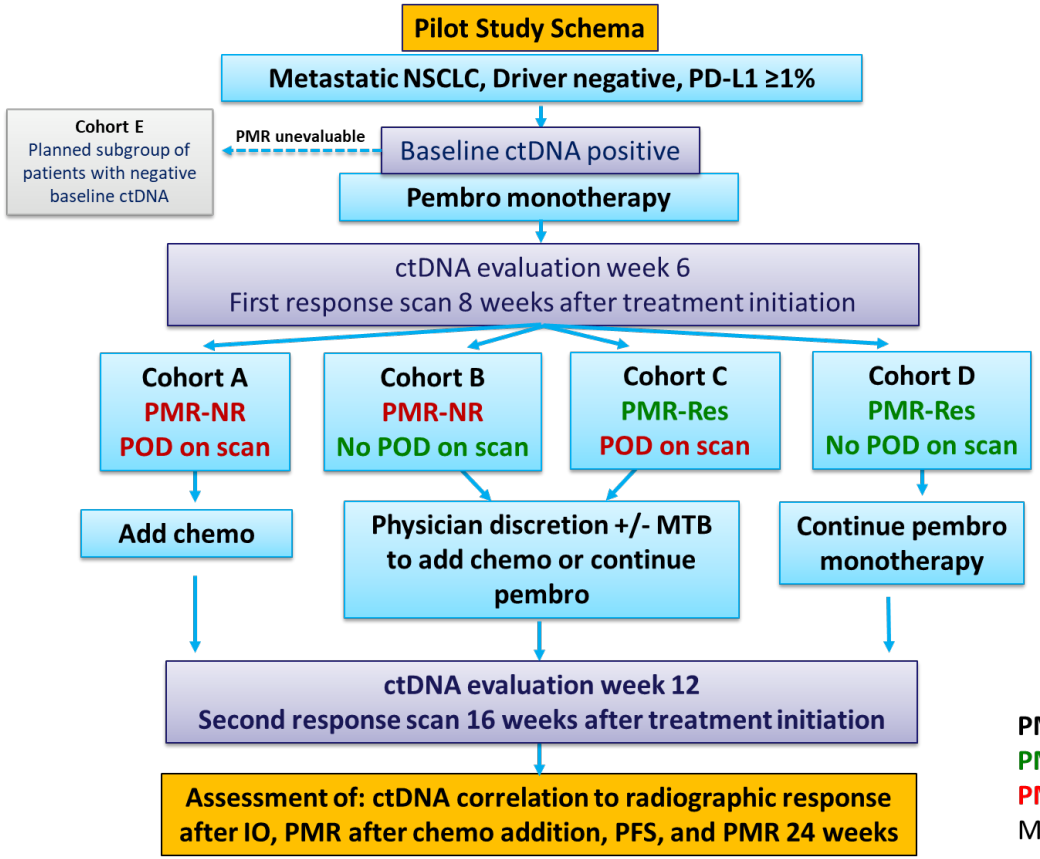
ctDNA dynamics reflect tumour burden (SLD) and response to therapy: IMpower150

CtDNA may serve as an important tool in clinical development and an early indicator of treatment benefit

Merino Vega et al (Allen J) JCO P), Aug 2022

CITAN: ctDNA-guided Immunotherapy-based Therapy in Treatment Naïve Advanced NSCLC

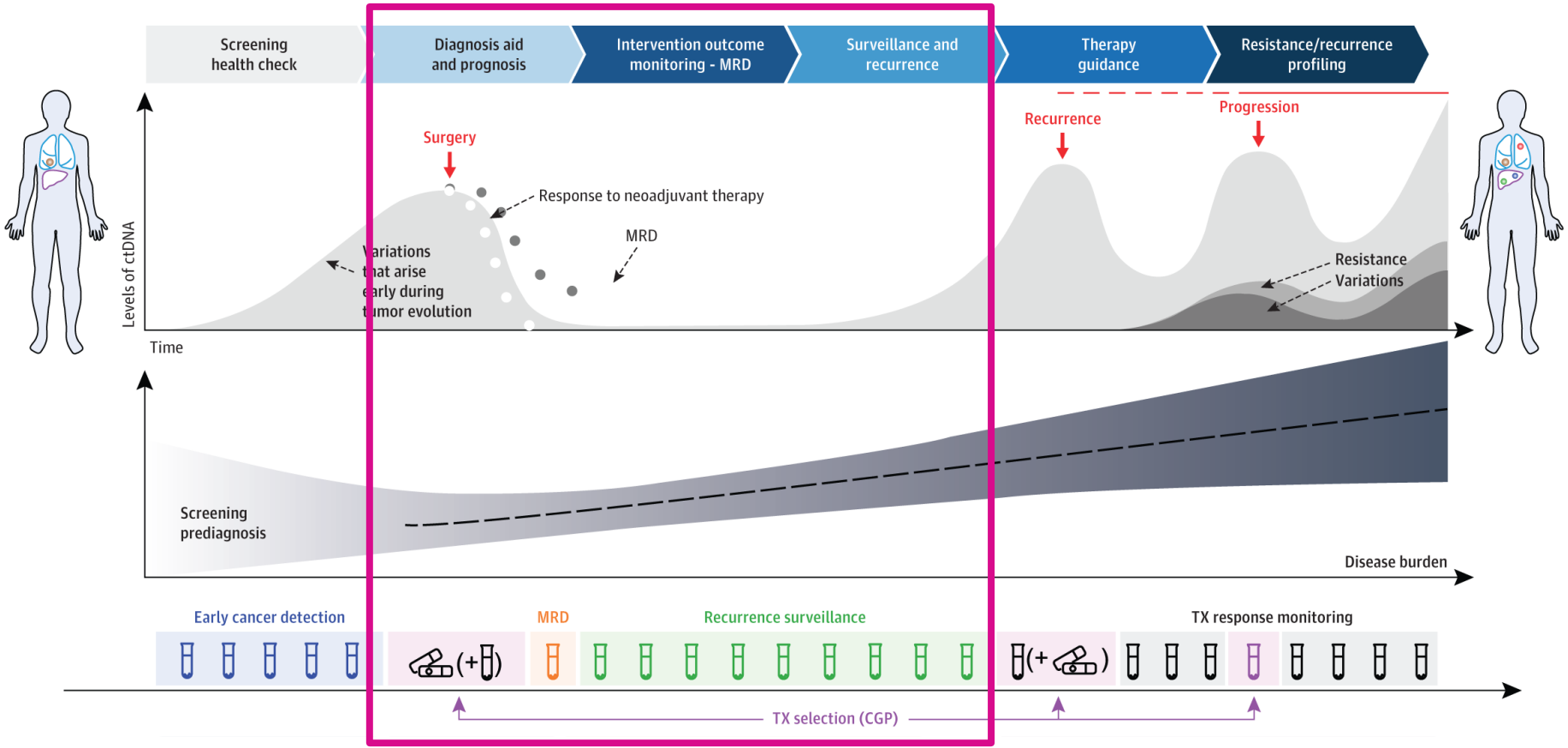
PI: Dr. Mack – Dr Rolfo



Translational Medicine Component

- **Baseline** Tissue, PBMCs
- **C2D1** ctDNA, PBMCs
- **C3D1** ctDNA, PBMCs
- **C4D1** ctDNA, PBMCs
- **Every 3 Cycles** ctDNA

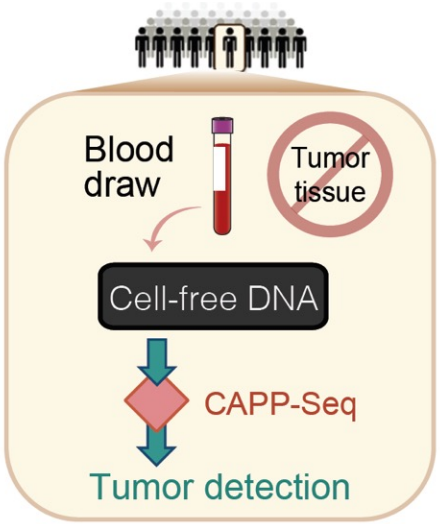
PMR = Plasma Molecular Response
PMR-Res = ≥50% PMR (responsive)
PMR-NR = <50% PMR (non-responsive)
MTB = Molecular Tumor Board



Krebs et al (Rolfo), JAMA Oncology OCT 2022

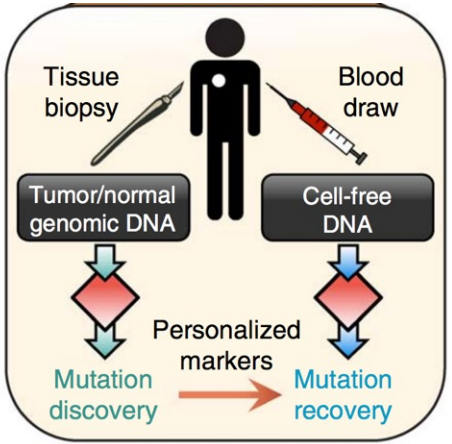
Different types of ctDNA MRD Assays

Tumor-naive



- Genotyping with no knowledge of tumor mutations (“off the shelf”)
- Faster, less expensive
- Limit of detection ~0.1%

Tumor-informed

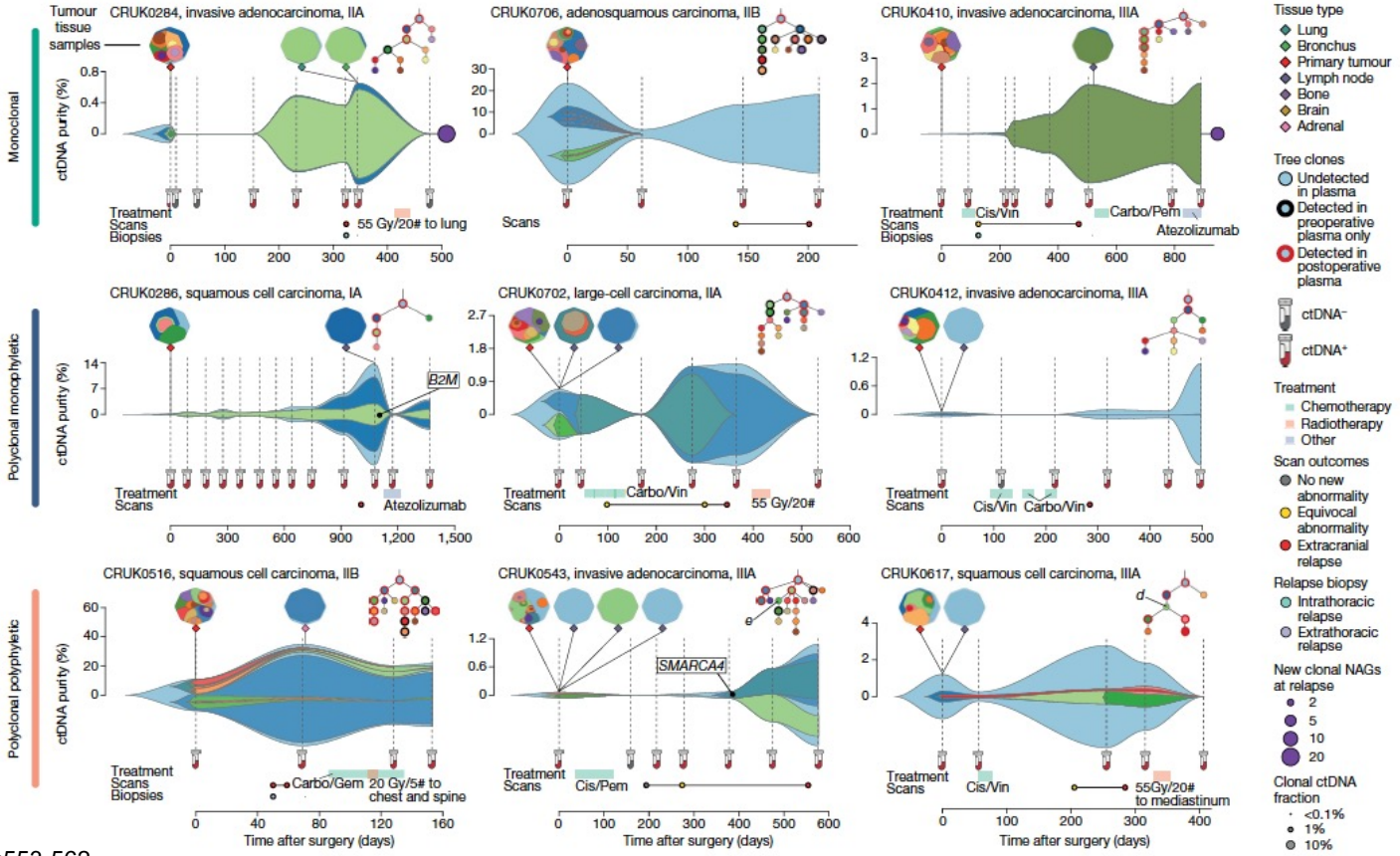


- Tracking multiple known mutations (bespoke or personalized)
- Requires tumor tissue, time, $$
- Limit of detection ~0.01%

Courtesy Dr. Natasha Leighl

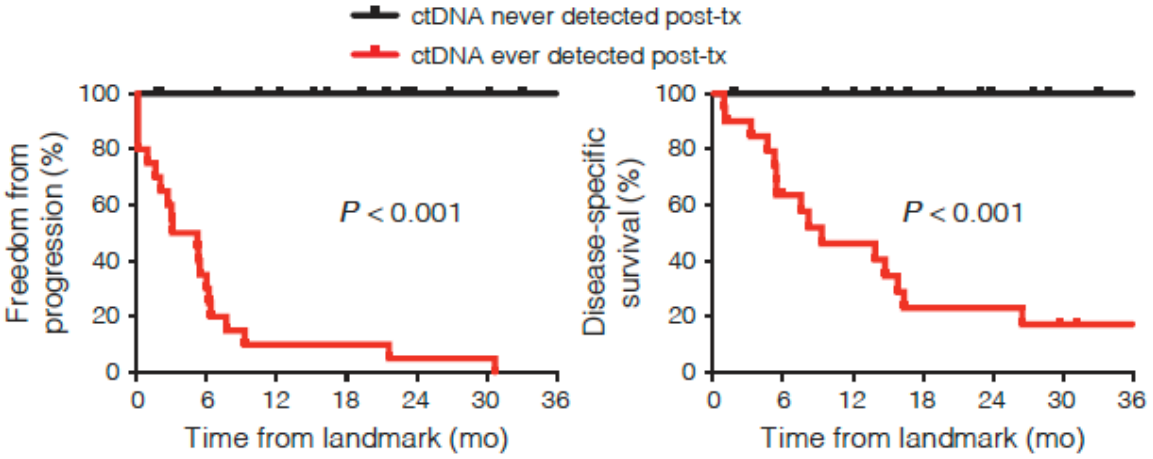
Longitudinal measurements of clonal evolution in the plasma from surgery to therapy and recurrence

Depictions of longitudinal tumour evolution for examples of monoclonal, polyclonal monophyletic and polyclonal polyphyletic metastatic dissemination patterns.

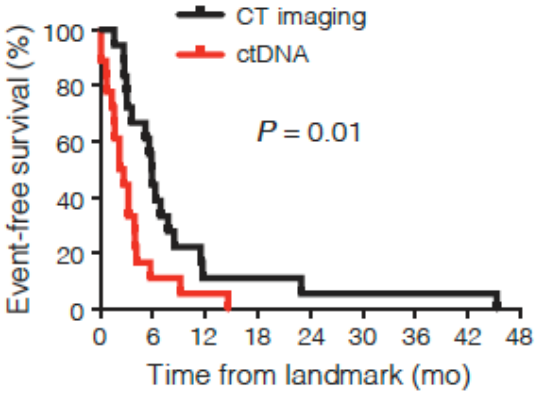


Abbosh C, et al. Nature. 2023 Apr;616(7957):553-562

Application of ctDNA analysis for posttreatment surveillance in patients with localised lung cancer



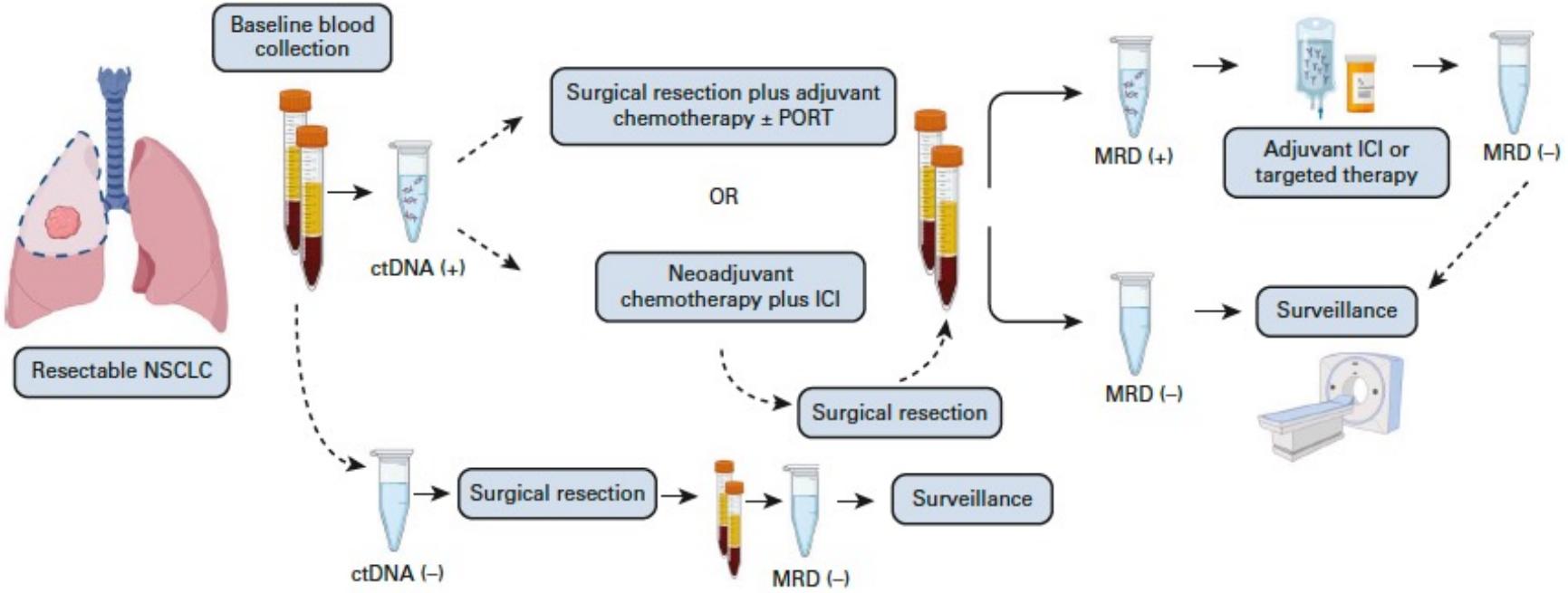
KM curves stratified by ctDNA detection status during posttreatment surveillance



ctDNA detection and time to imaging progression

Chaudhuri AA, *et al. Cancer Discov* 2017;7(12):1394-1403.

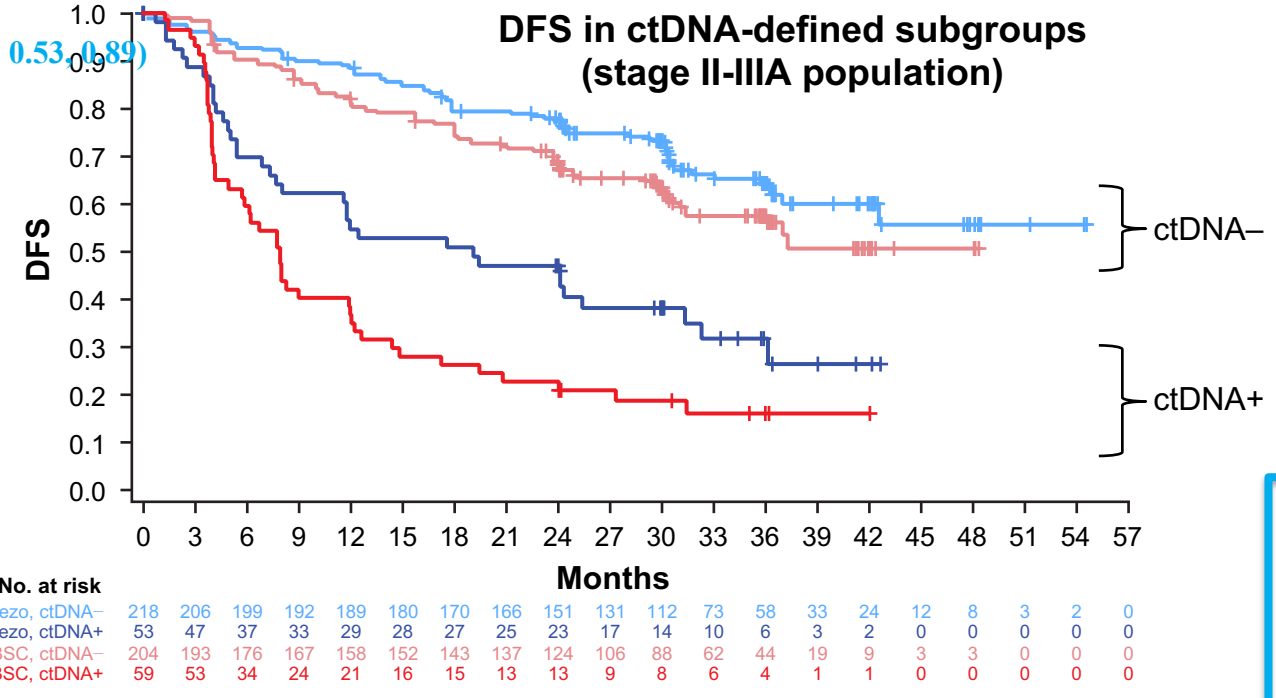
Proposed clinical trial designs for early-stage NSCLC using ctDNA as a biomarker for treatment personalization



Pellini B & Chaudhuri AA. JCO 2022

ctDNA positivity was strongly prognostic, with DFS favouring atezo in both ctDNA+ and ctDNA– patients

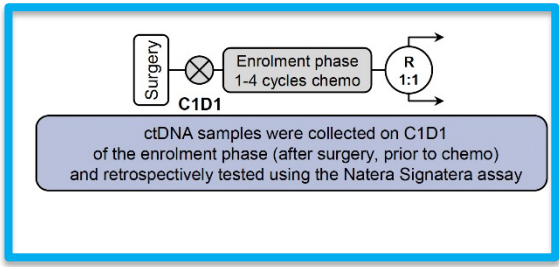
In all ctDNA-evaluable stage II-IIIA patients, mDFS was NR (atezo) vs 31.4 months (BSC), with an HR of 0.69 (95% CI:



ctDNA–	Atezo (n=218)	BSC (n=204)
mDFS, mo	NR	NR
HR (95% CI)	0.72 (0.52, 1.00)	

ctDNA+	Atezo (n=53)	BSC (n=59)
mDFS, mo	19.1	7.9
HR (95% CI)	0.61 (0.39, 0.94)	

Plasma collection for ctDNA analysis



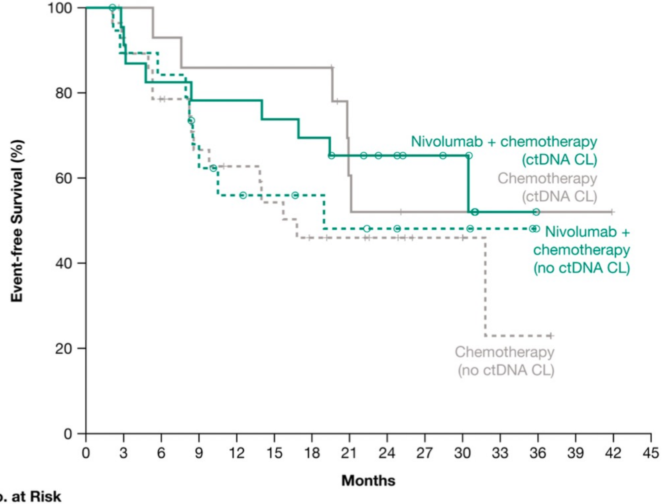
C. Zhou, ESMO 2021

Clinical cutoff: 21 January 2021. Unstratified HRs are shown.

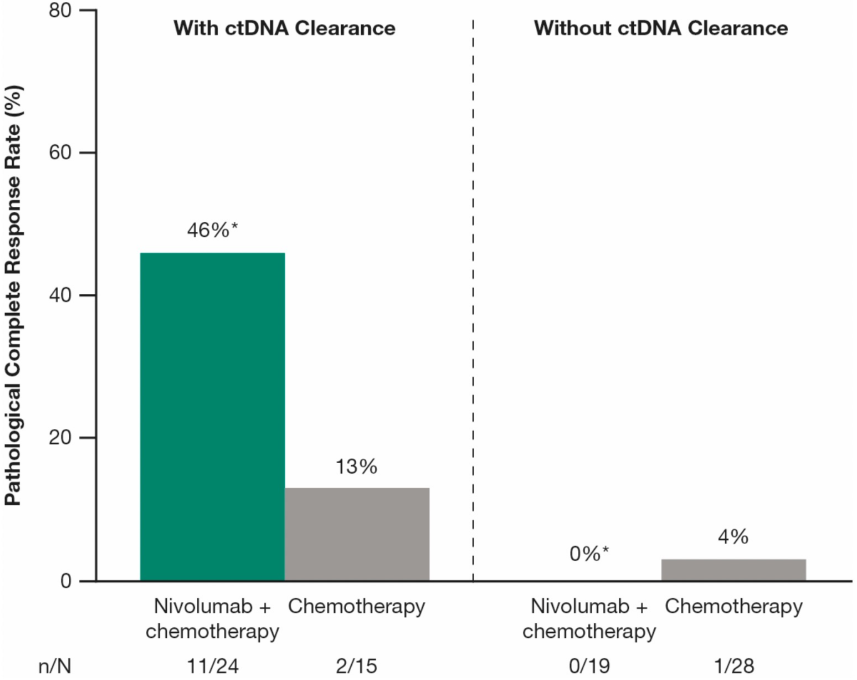
Liquid Biopsy in Neoadjuvant IO + chemo combination

WES ctDNA in 89 pts

	Nivolumab + chemotherapy		Chemotherapy	
	ctDNA CL (n=24)	No ctDNA CL (n=19)	ctDNA CL (n=15)	No ctDNA CL (n=28)
Median EFS, mo (95% CI)	NR (16.8–NR)	18.9 (8.3–NR)	NR (19.6–NR)	16.8 (8.3–NR)
HR (95% CI)	0.60 (0.20–1.82)		0.63 (0.20–2.01)	



No. at Risk																
Nivolumab + chemotherapy (ctDNA CL)	24	21	19	18	18	17	16	13	11	8	7	1	0	0	0	0
Chemotherapy (ctDNA CL)	15	14	13	12	12	12	12	7	6	5	5	5	3	1	0	0
Nivolumab + chemotherapy (no ctDNA CL)	19	17	16	12	9	8	7	6	5	3	3	2	0	0	0	0
Chemotherapy (no ctDNA CL)	28	26	21	17	15	13	10	9	7	4	3	1	1	0	0	0



Forde P. et al, NEJM, AACR 2022 Courtesy Dr. Natasha Leig

Take Home Message

- Liquid and tissue biopsy have a high concordance
- Liquid Biopsy is a great tool for real time monitoring in advance disease
- Liquid Biopsy is a perfect tool for MRD
- Tissue informed approach advantage , but also limitations
- Integrating liquid biopsy in clinical trials is a necessity

Join us in 2023 Madrid, Spain

ISLB
INTERNATIONAL SOCIETY OF LIQUID BIOPSY

5TH ANNUAL CONGRESS
Liquid Biopsy
19 - 21 November 2023 | Madrid, Spain

Save the Date
19-21, November 2023