City of Hope®

Precision Medicine in Metastatic NSCLC

Ravi Salgia, MD, PhD

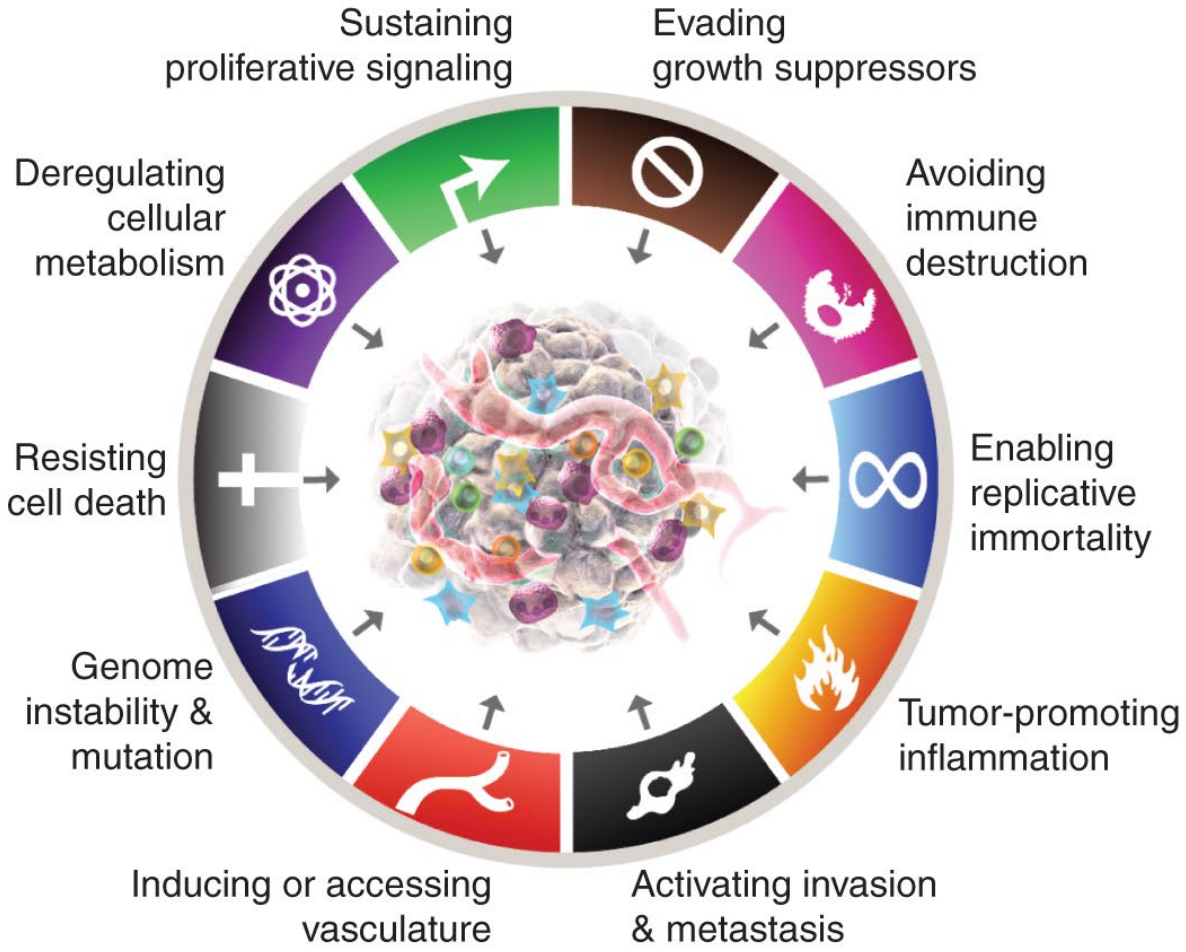
Professor and Chair

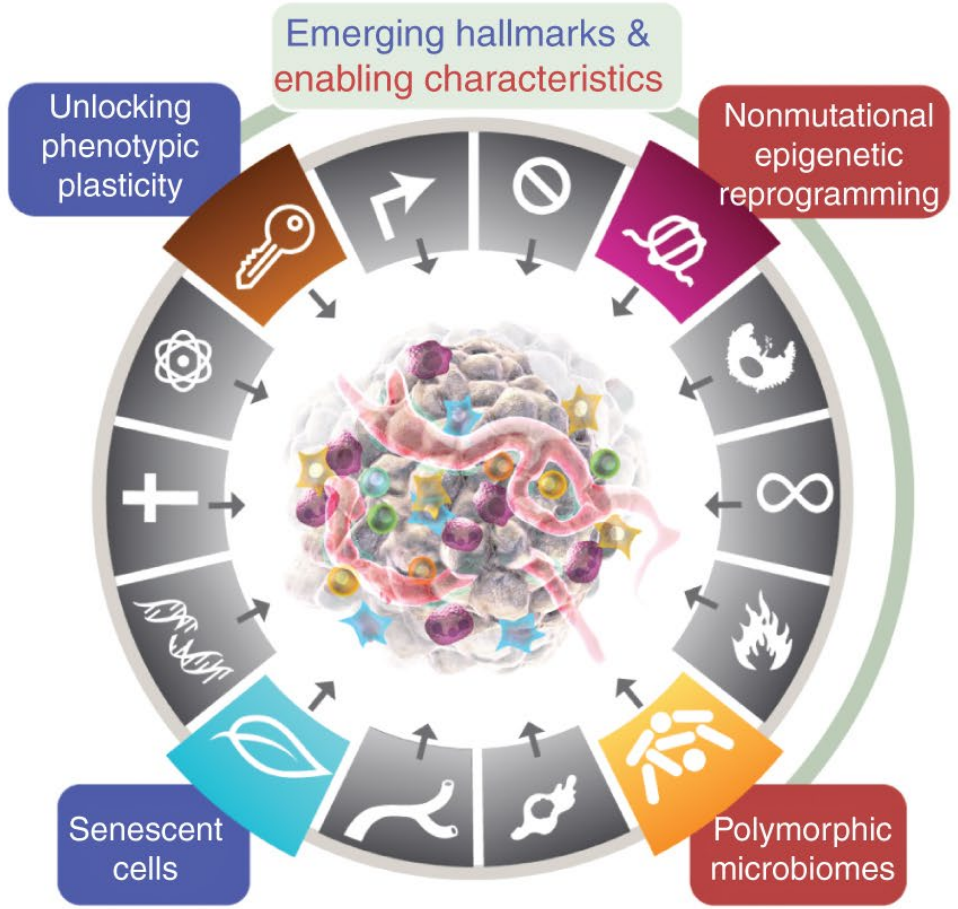
Department of Medical Oncology and Therapeutics Research

Objectives

- Precision Medicine at City of Hope
- Lung Cancer Overview
- Precision Medicine Overview
- Therapeutic Strategies
- Germline Testing and Strategies
- Artificial Intelligence for Precision Medicine

Hallmarks of Cancer: New Dimensions





Hanahan, Cancer Discov, 2022

City of Hope®

CHICAGO, IL

LOS ANGELES, CA

ORANGE COUNTY, CA

tgen

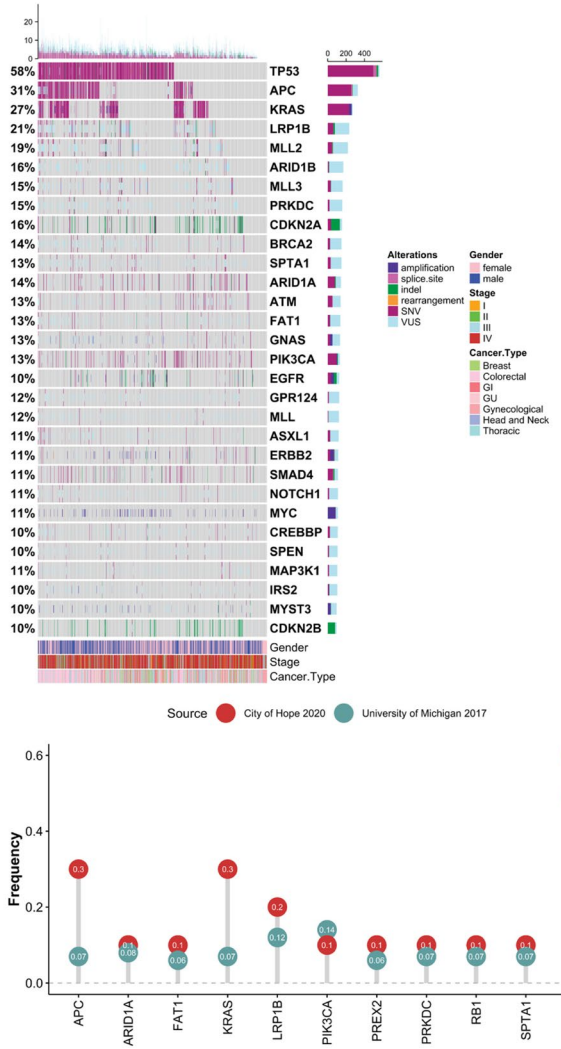
PHOENIX, AZ

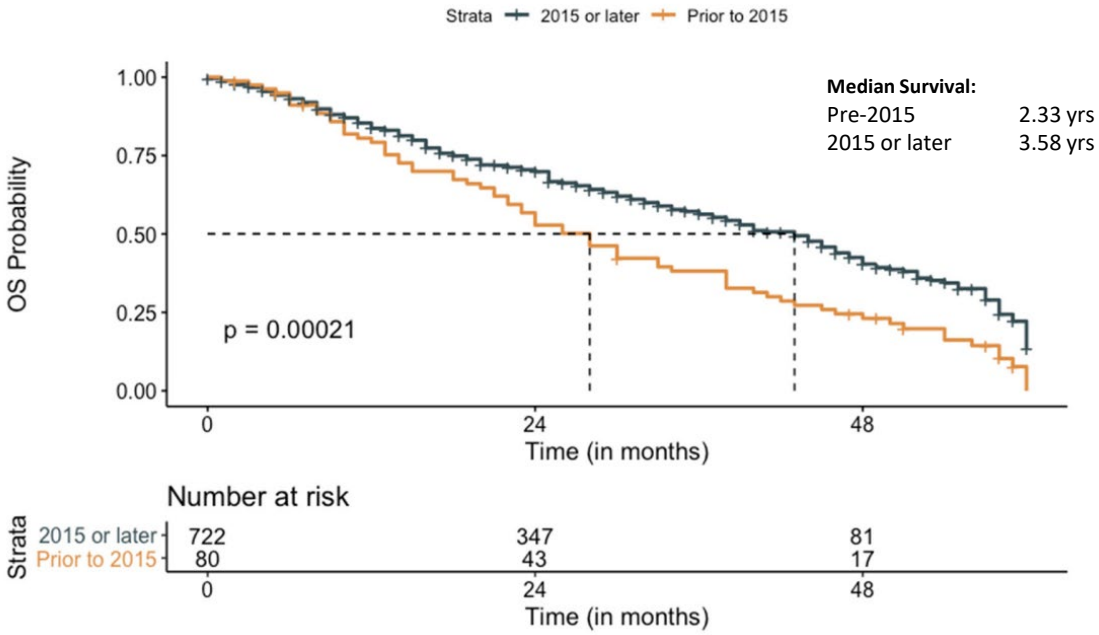
ATLANTA, GA

City of Hope, a world-renowned, National Cancer Institute-designated comprehensive cancer center, now has one of the largest geographic footprints in cancer research and treatment, providing cancer patients with timely access to exceptional care, clinical trials and leading-edge innovation.

City of Hope main site TGen Clinical network sites

Precision Medicine in Solid Tumors at COH



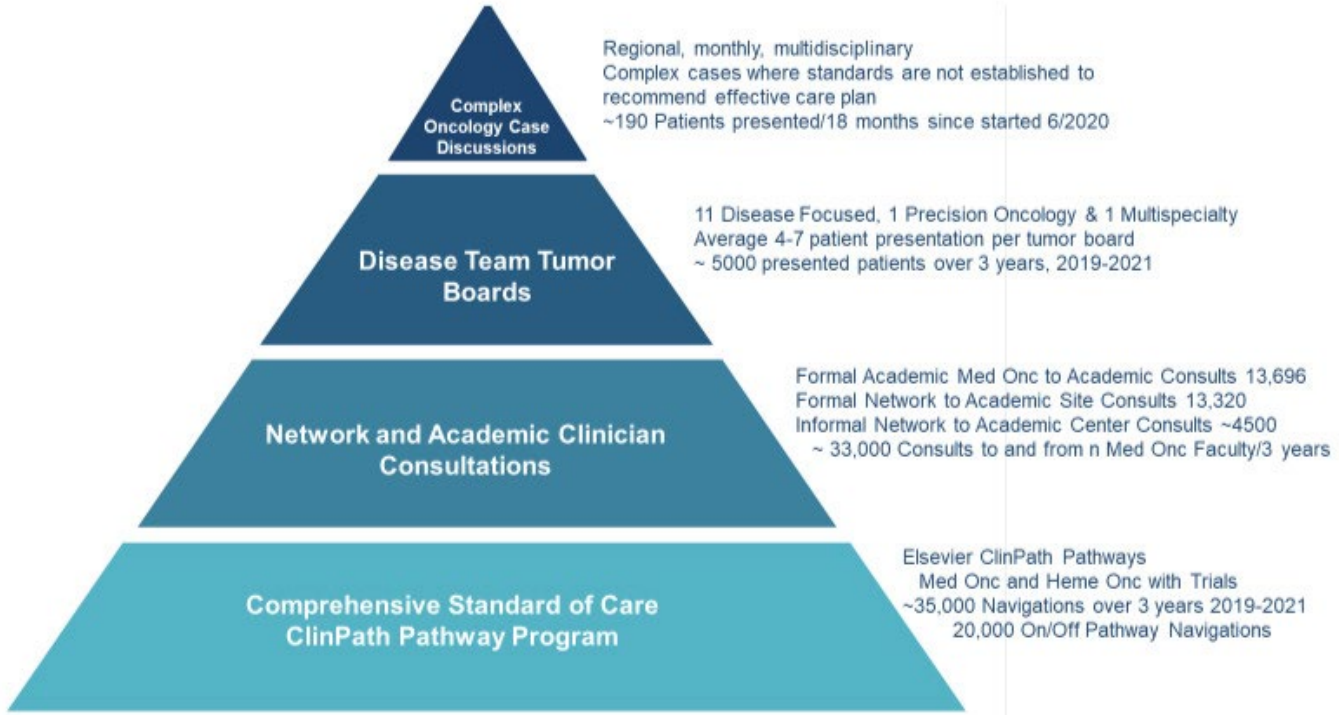


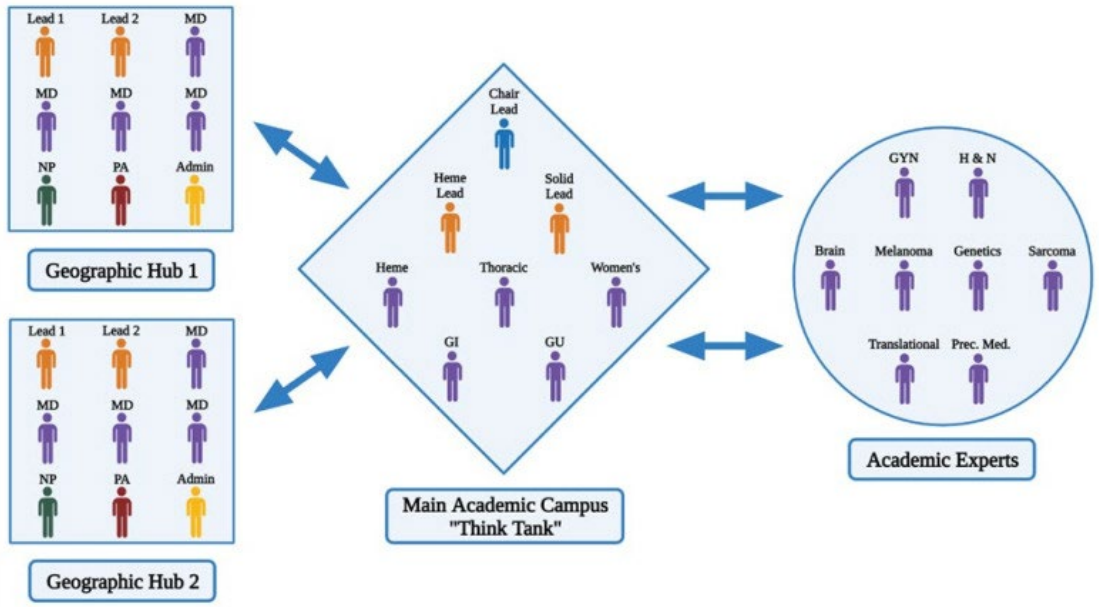
Median Survival:

Pre-2015	2.33 yrs
2015 or later	3.58 yrs

Roosan et int. Salgia, Cancers, 2021

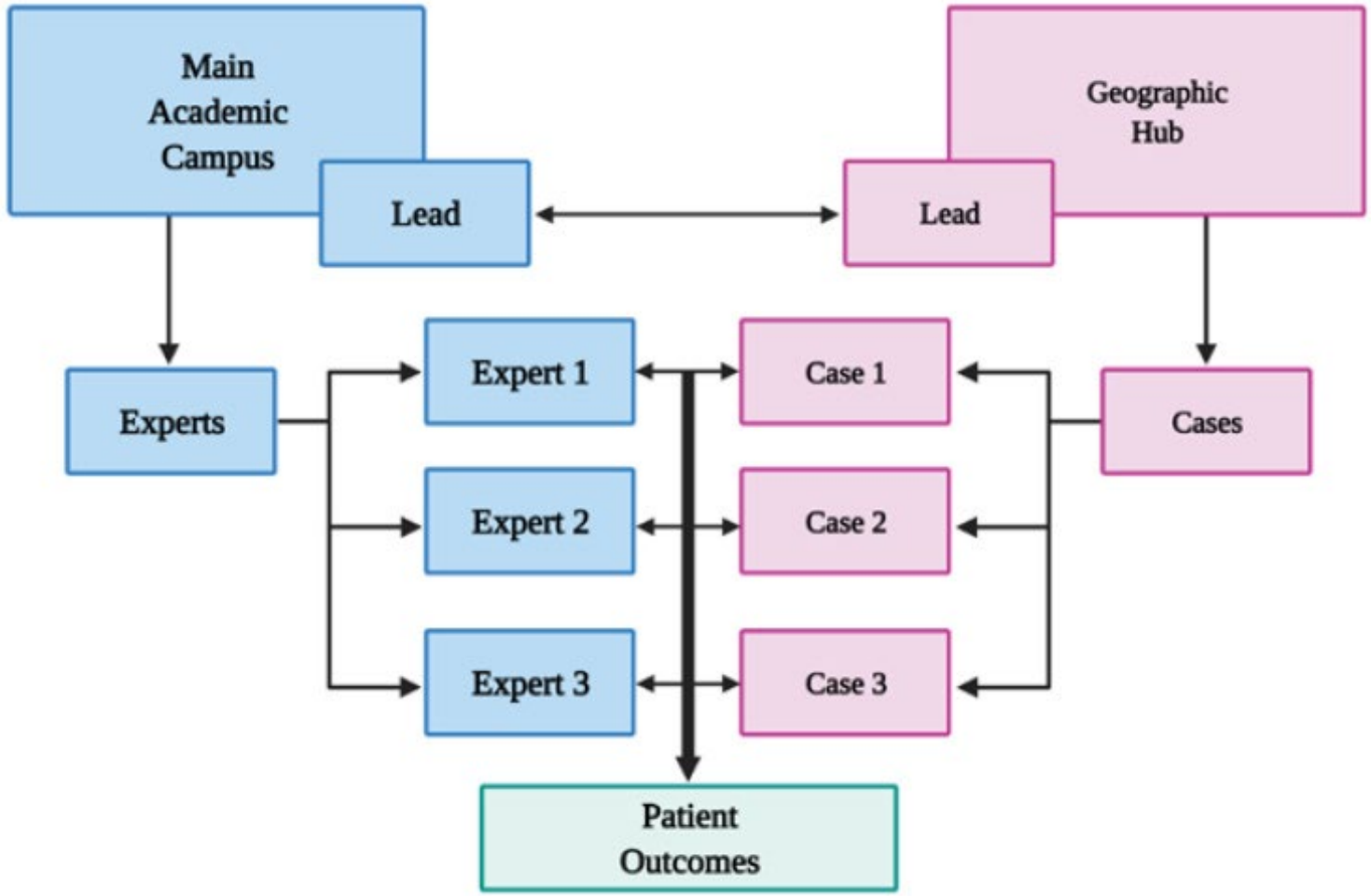
COH Enterprise: Decision Support Network





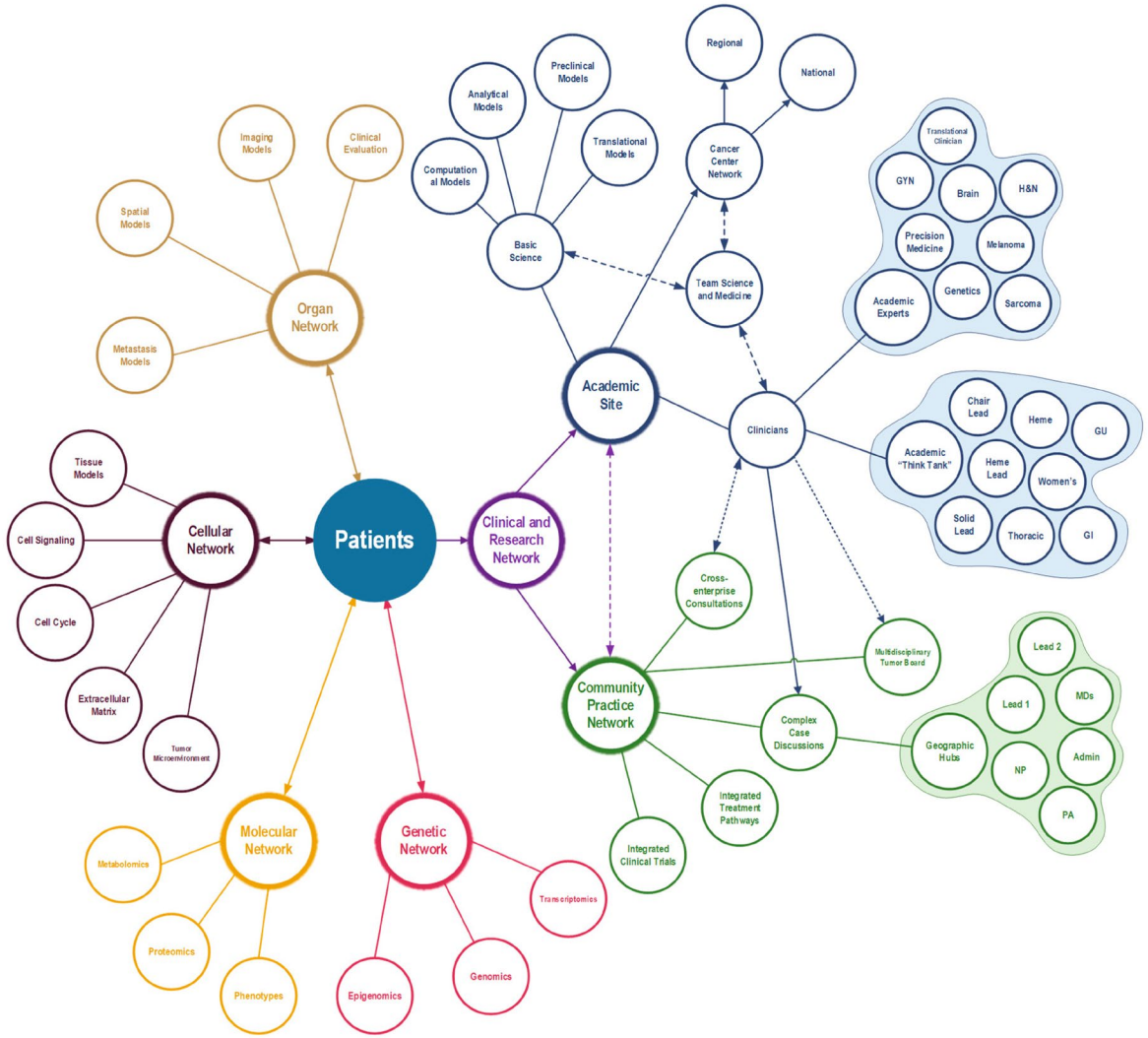
Bosserman et int. Salgia, JCM, 2022

Complex Oncology Case Discussion Algorithm- Academic and Geographic Network



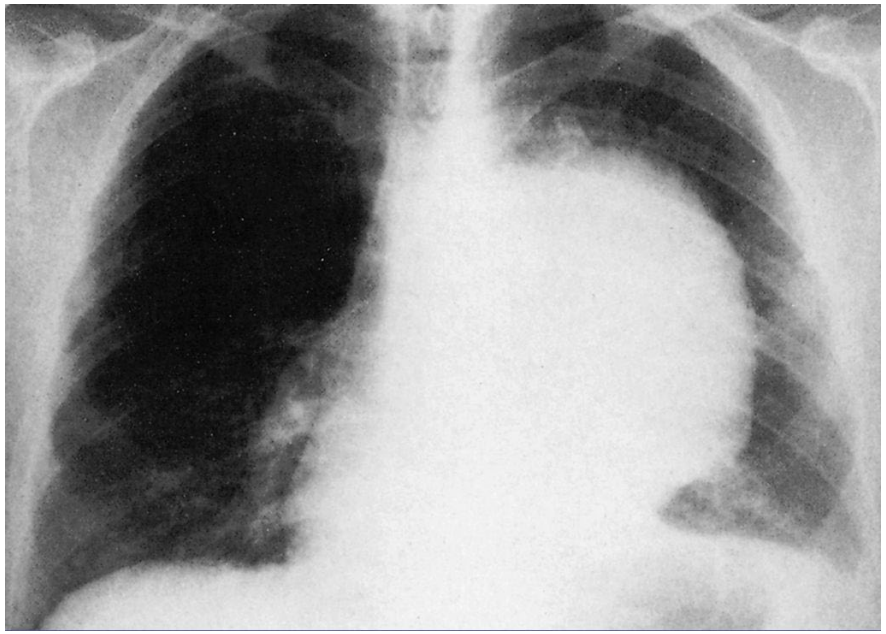
Bosserman et int. Salgia, JCM, 2022

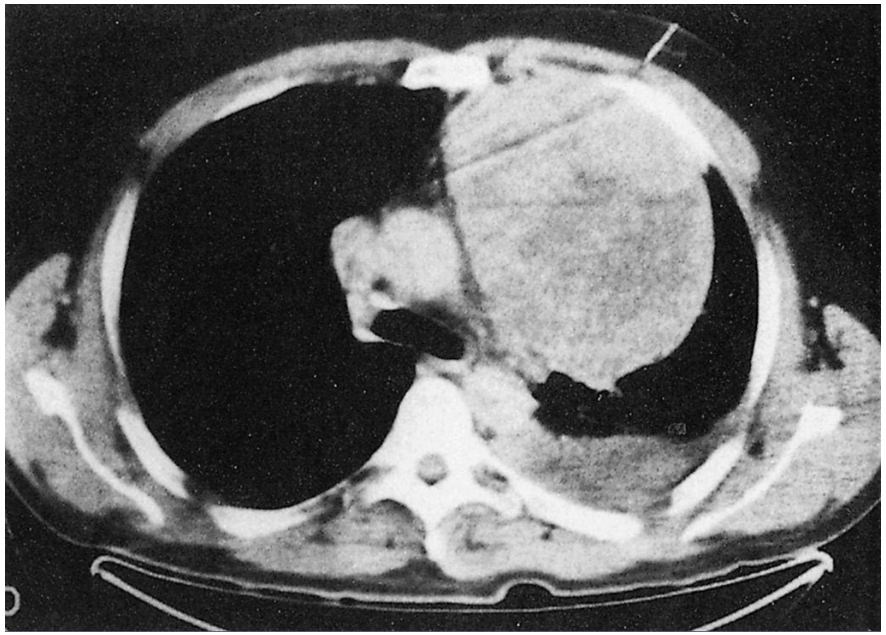
Enhancing the Patient Network

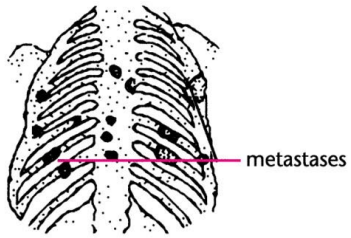


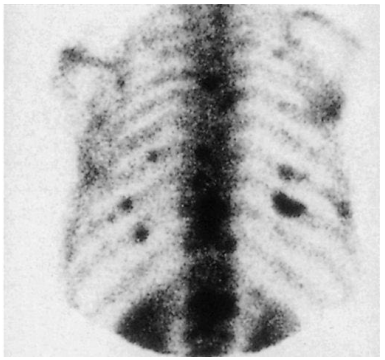
Mambetsariev, Fricke, et int. Salgia, JCM, 2023

Lung Cancer







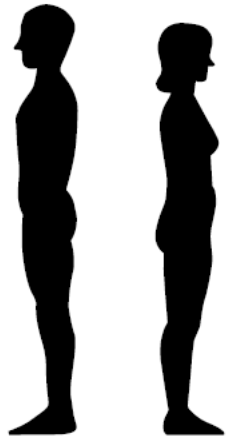


Salgia et al., 2010

Lung Cancer Incidence and Mortality

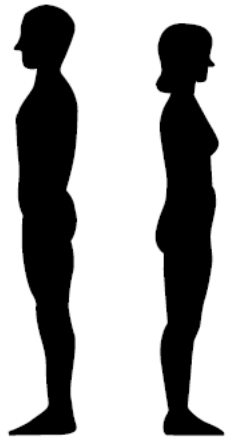
Estimated New Cases

Male			Female		
Prostate	299,010	29%	Breast	310,720	32%
Lung & bronchus	116,310	11%	Lung & bronchus	118,270	12%
Colon & rectum	81,540	8%	Colon & rectum	71,270	7%
Urinary bladder	63,070	6%	Uterine corpus	67,880	7%
Melanoma of the skin	59,170	6%	Melanoma of the skin	41,470	4%
Kidney & renal pelvis	52,380	5%	Non-Hodgkin lymphoma	36,030	4%
Non-Hodgkin lymphoma	44,590	4%	Pancreas	31,910	3%
Oral cavity & pharynx	41,510	4%	Thyroid	31,520	3%
Leukemia	36,450	4%	Kidney & renal pelvis	29,230	3%
Pancreas	34,530	3%	Leukemia	26,320	3%
All sites	**1,029,080**		**All sites**	**972,060**	



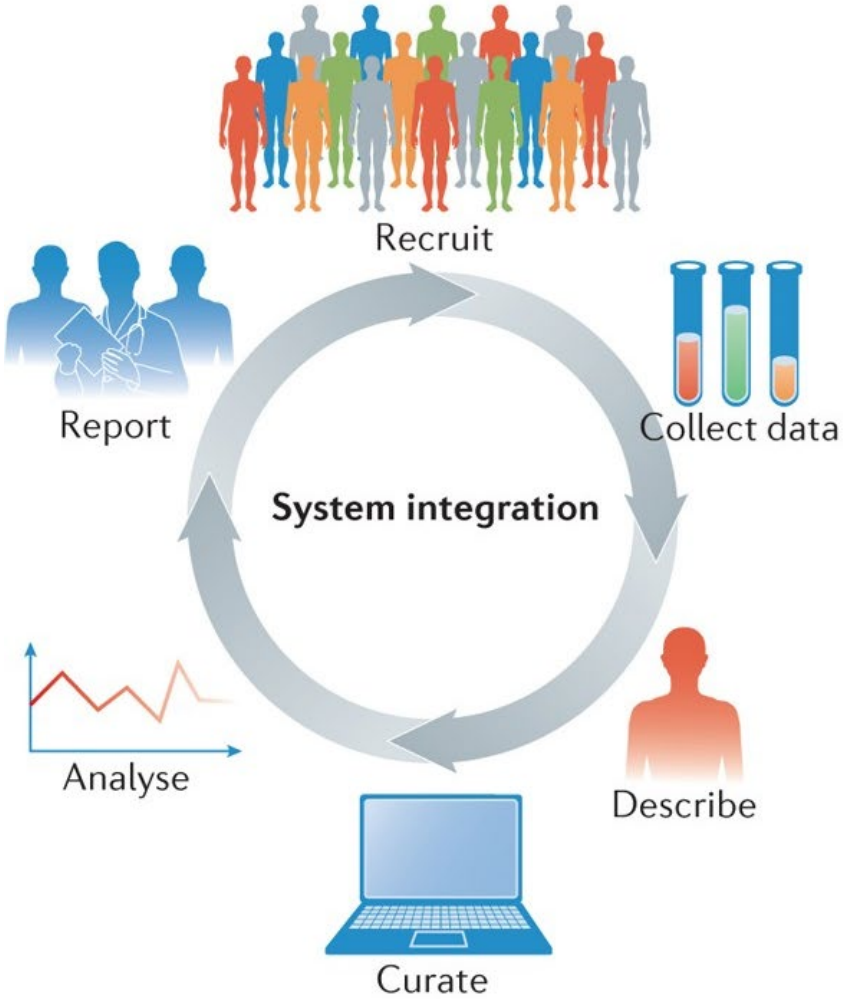
Estimated Deaths

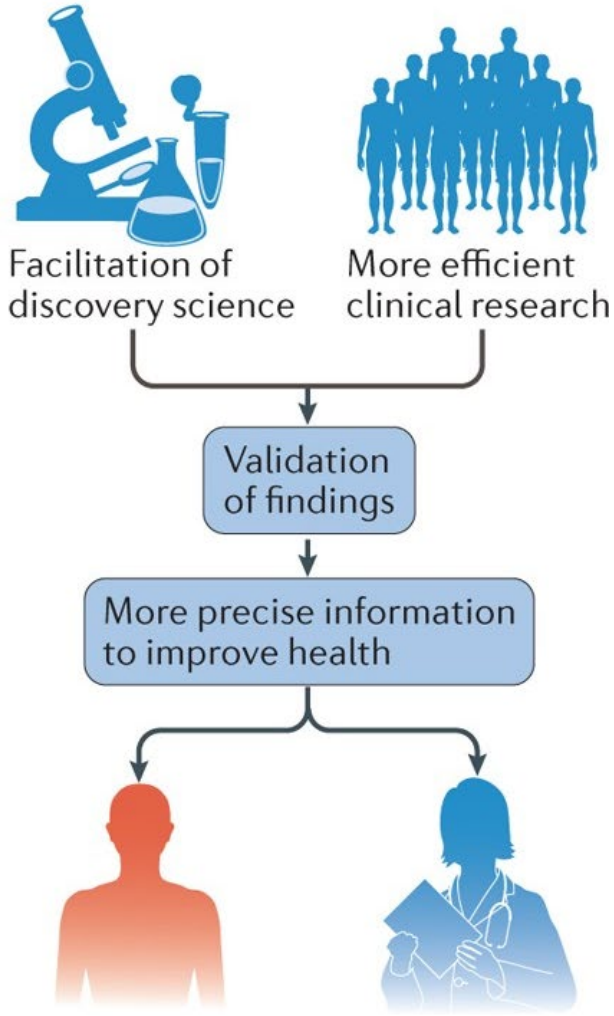
Male			Female		
Lung & bronchus	65,790	20%	Lung & bronchus	59,280	21%
Prostate	35,250	11%	Breast	42,250	15%
Colon & rectum	28,700	9%	Pancreas	24,480	8%
Pancreas	27,270	8%	Colon & rectum	24,310	8%
Liver & intrahepatic bile duct	19,120	6%	**Uterine corpus**	**13,250**	**5%**
Leukemia	13,640	4%	Ovary	12,740	4%
Esophagus	12,880	4%	Liver & intrahepatic bile duct	10,720	4%
Urinary bladder	12,290	4%	Leukemia	10,030	3%
Non-Hodgkin lymphoma	11,780	4%	Non-Hodgkin lymphoma	8,360	3%
Brain & other nervous system	10,690	3%	Brain & other nervous system	8,070	3%
All sites	**322,800**		**All sites**	**288,920**	



Siegel et al., CA Cancer J. Clin., 2024

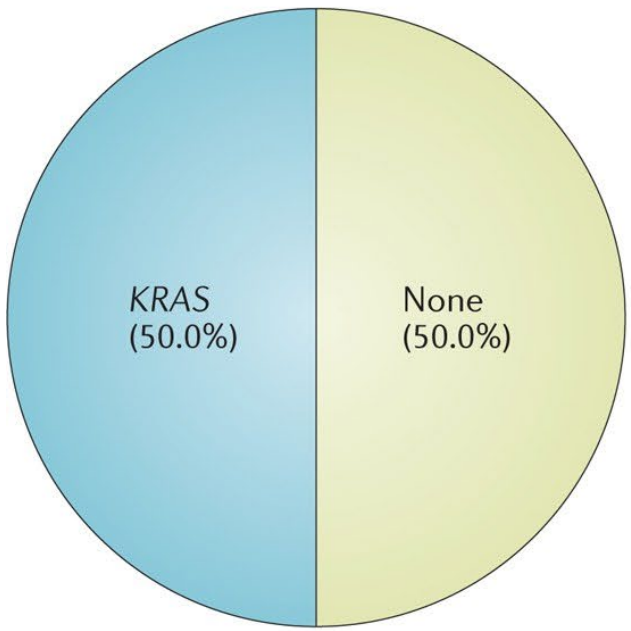
Precision Medicine System and Goals



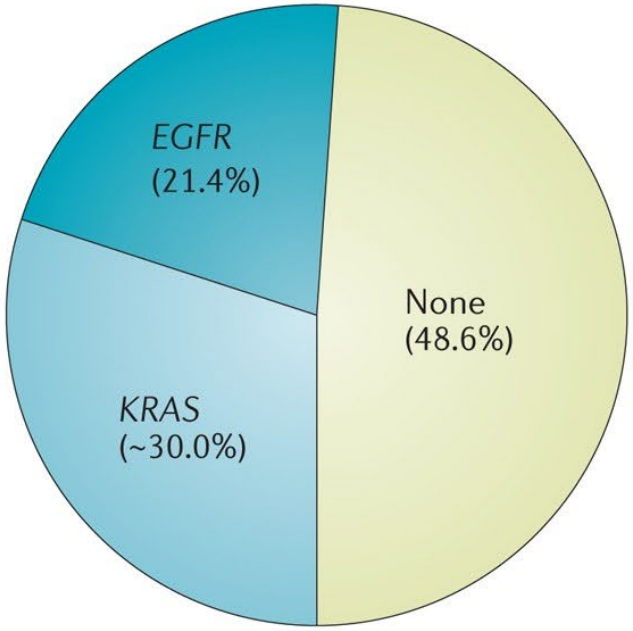


Antman and Loscalzo, Nature Reviews Cardiology, 2016

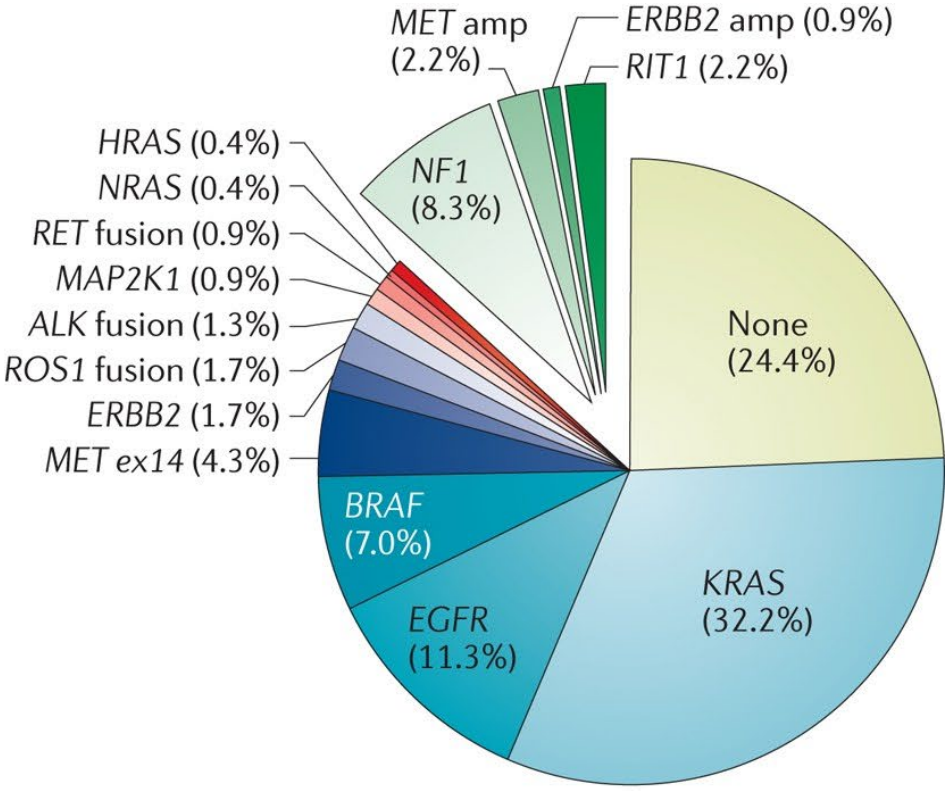
Lung Cancer Genomic Knowledge Has Evolved



1987



2004



2014

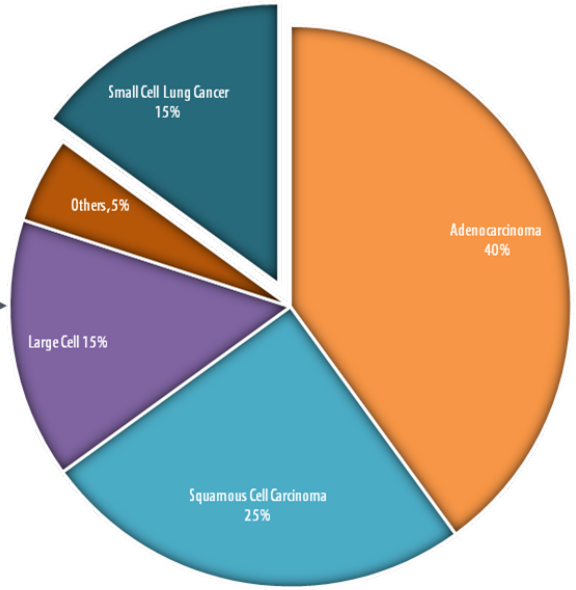
Vargas and Harris, Nature Reviews Cancer, 2016

Lung Cancer- Therapeutic Evolution

Historical

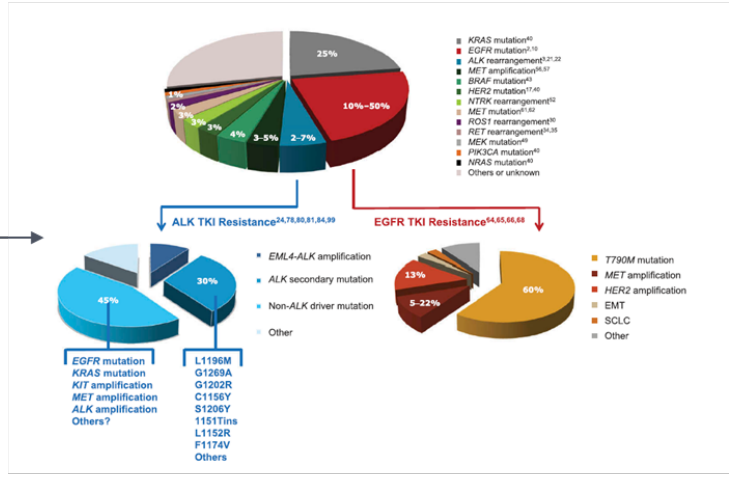
Few, if any treatment options

Lung Cancer Subtypes



Chemotherapy

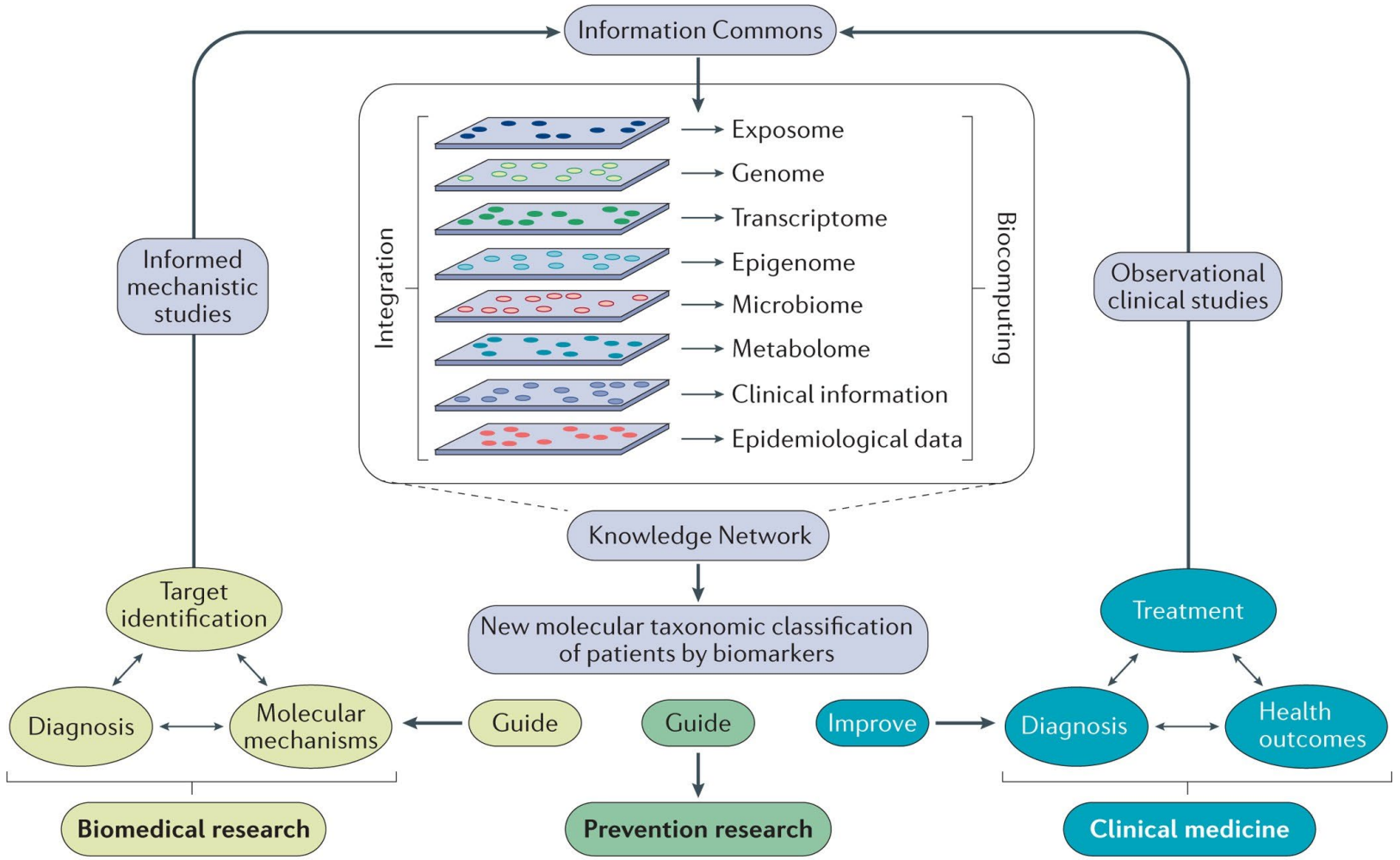
Precision Medicine



Many targeted therapies

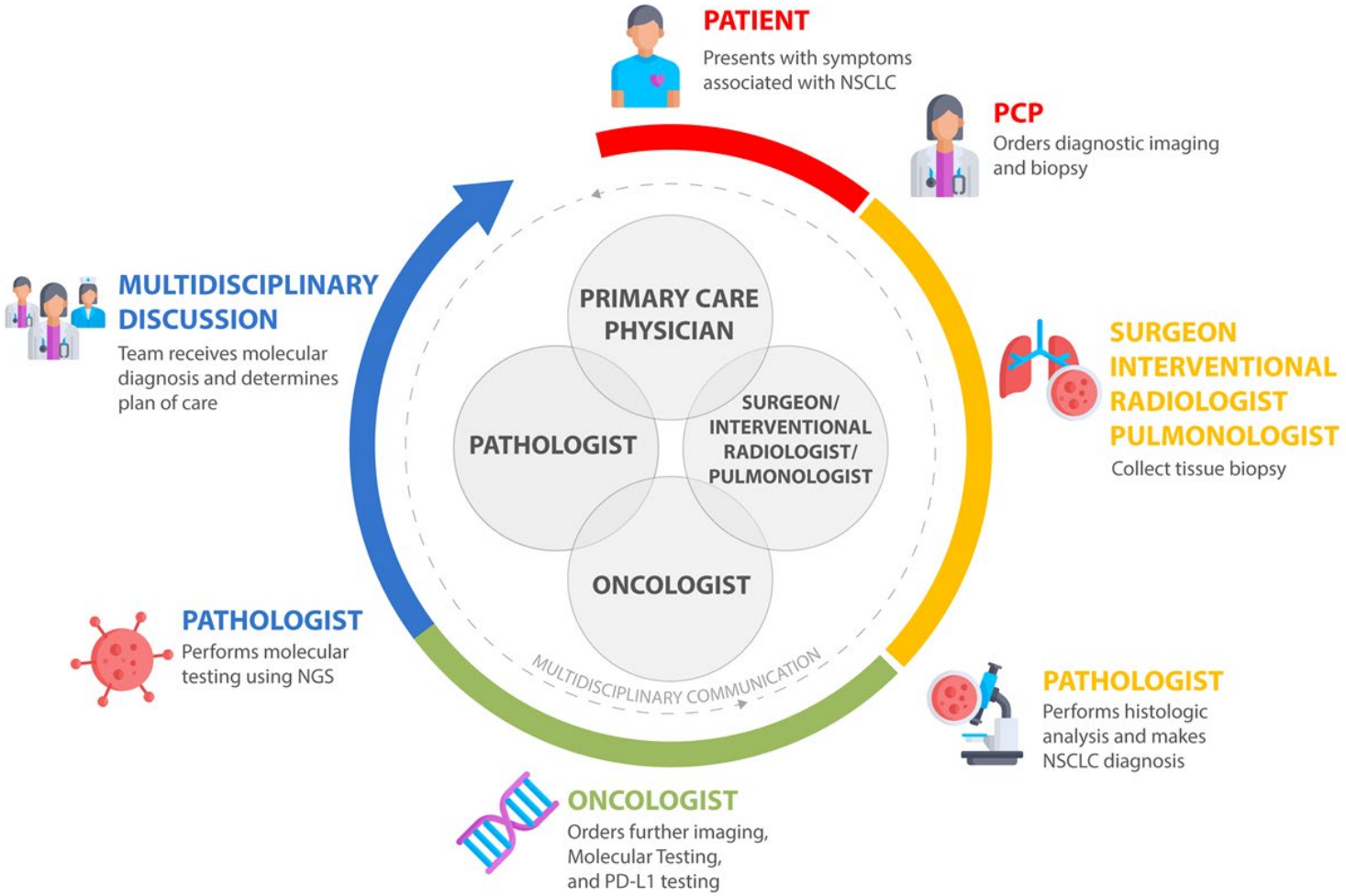
Salgia, 2019

Lung Cancer- Precision Medicine Strategy



Vargas and Harris, Nature Reviews Cancer, 2016

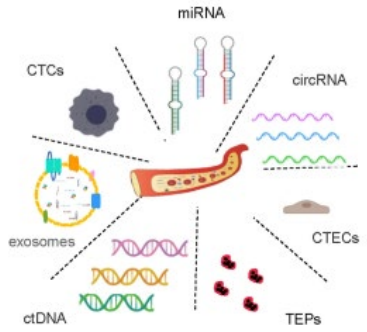
Precision Medicine Multidisciplinary Care Model



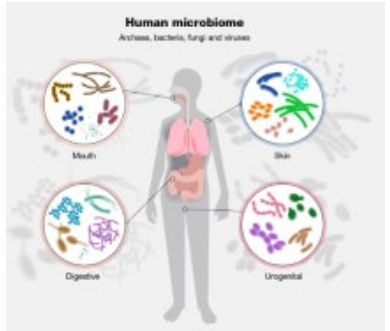
Salgia and Mambetsariev, J. Clin. Med., 2020

Precision Medicine Tools

Tissue Genomics

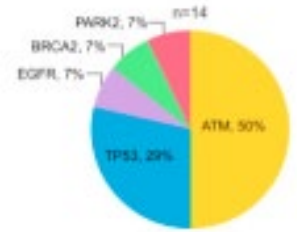


Liquid Biopsy



Microbiome Analysis

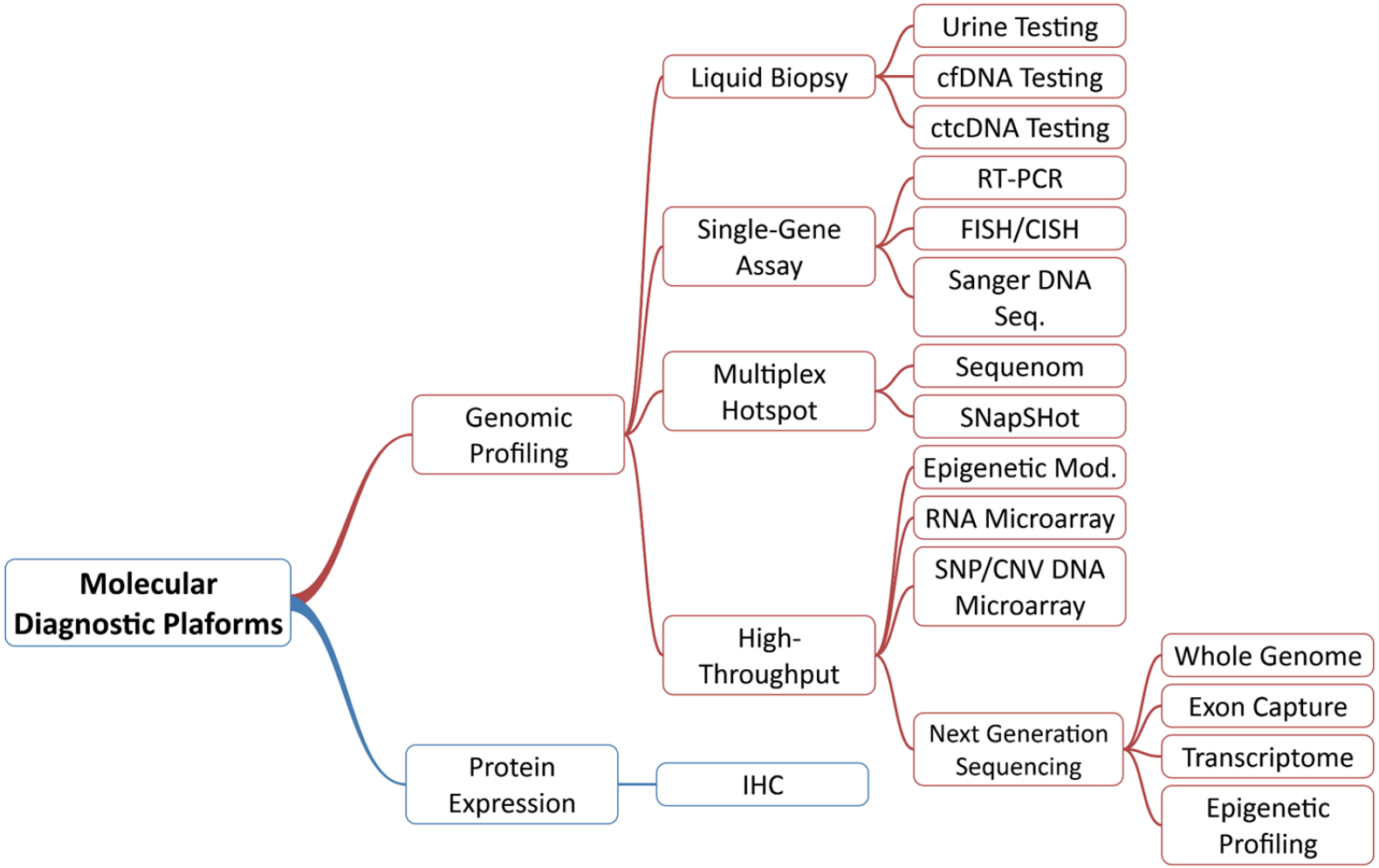
City of Hope Medical Oncology



Germline Genomics

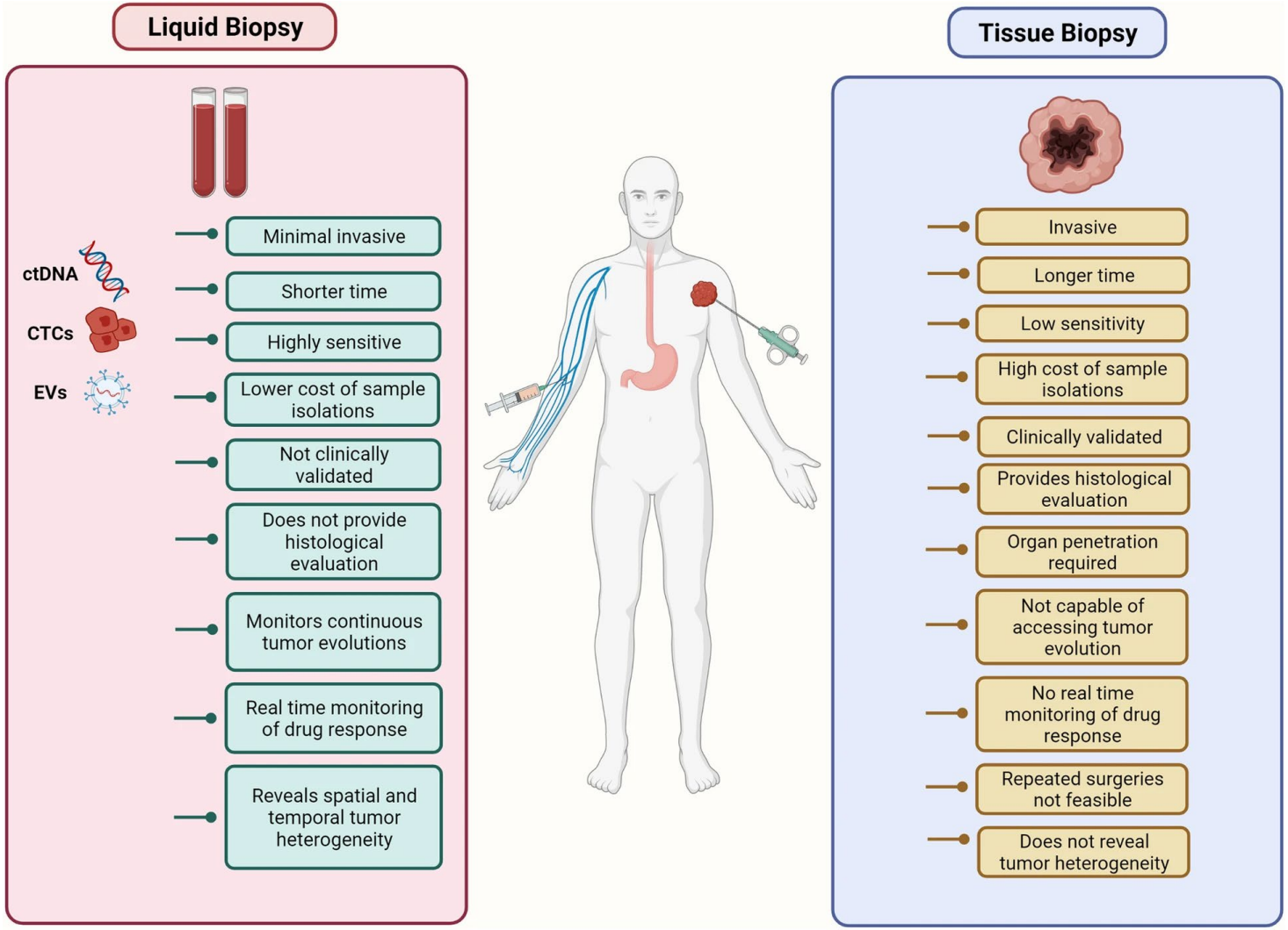
Salgia, 2024

Precision Medicine- Diagnostic Platform Options



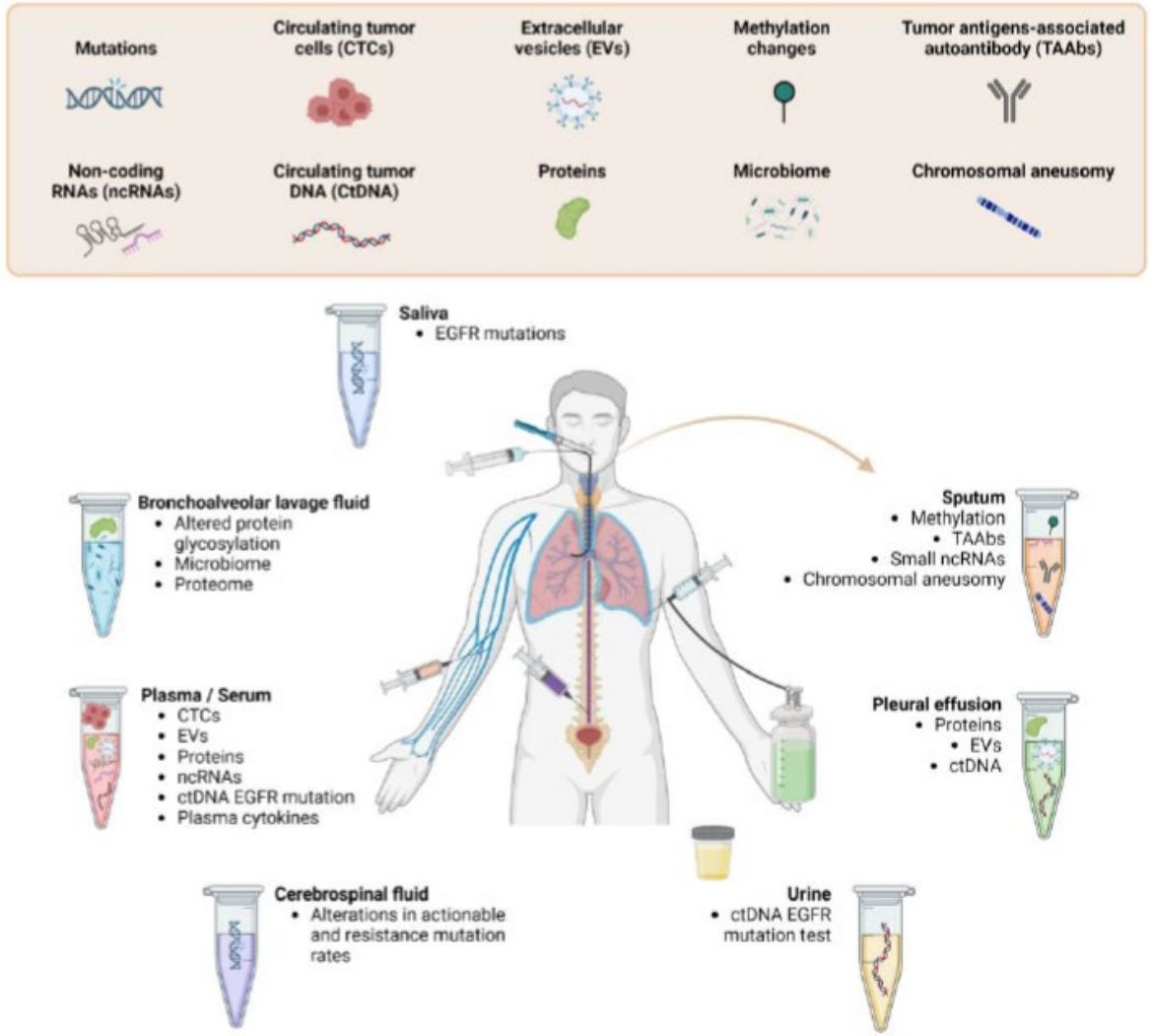
Hensing, Mambetsariev, Salgia; 2017; in Pass et al. IASLC Thoracic Oncology 2nd Ed.

Liquid Biopsy Versus Tissue Biopsy



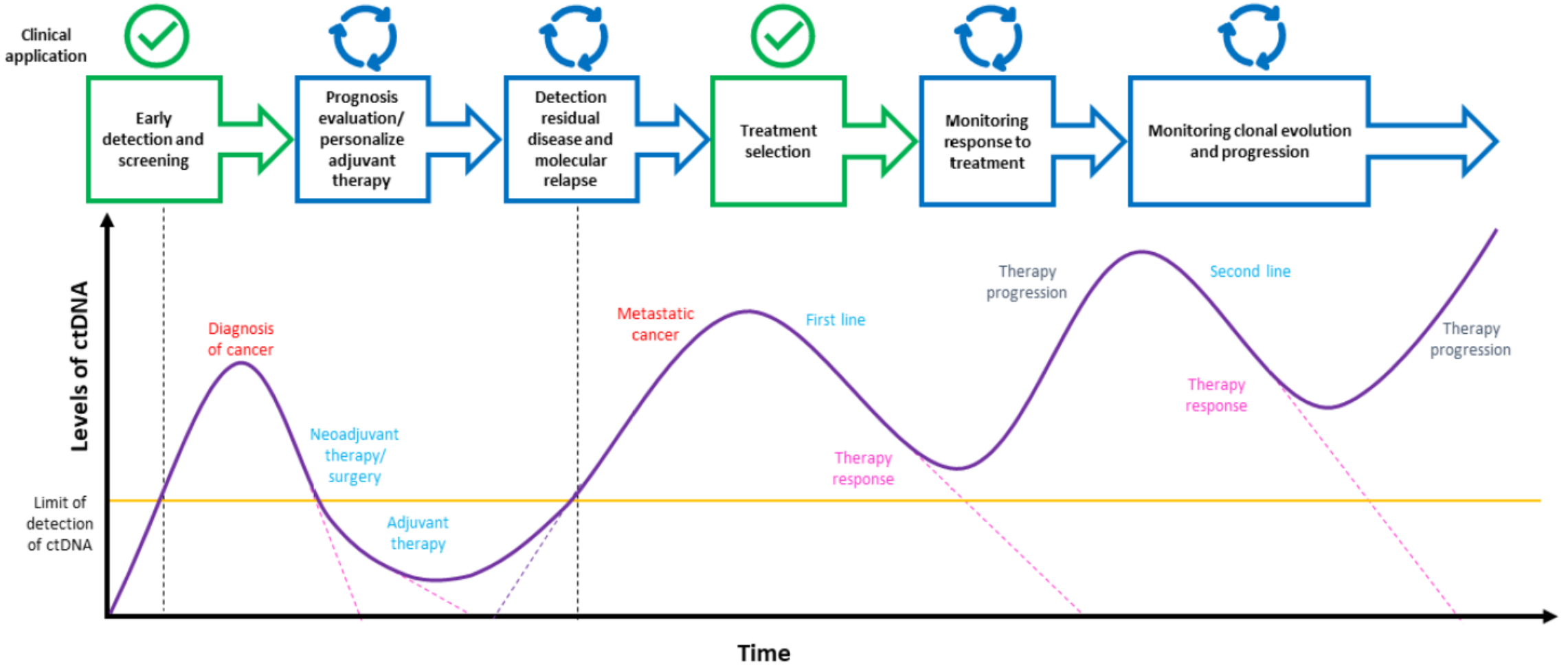
Lone et al., Mol Cancer, 2022

Utility of Liquid Biopsy in Cancer



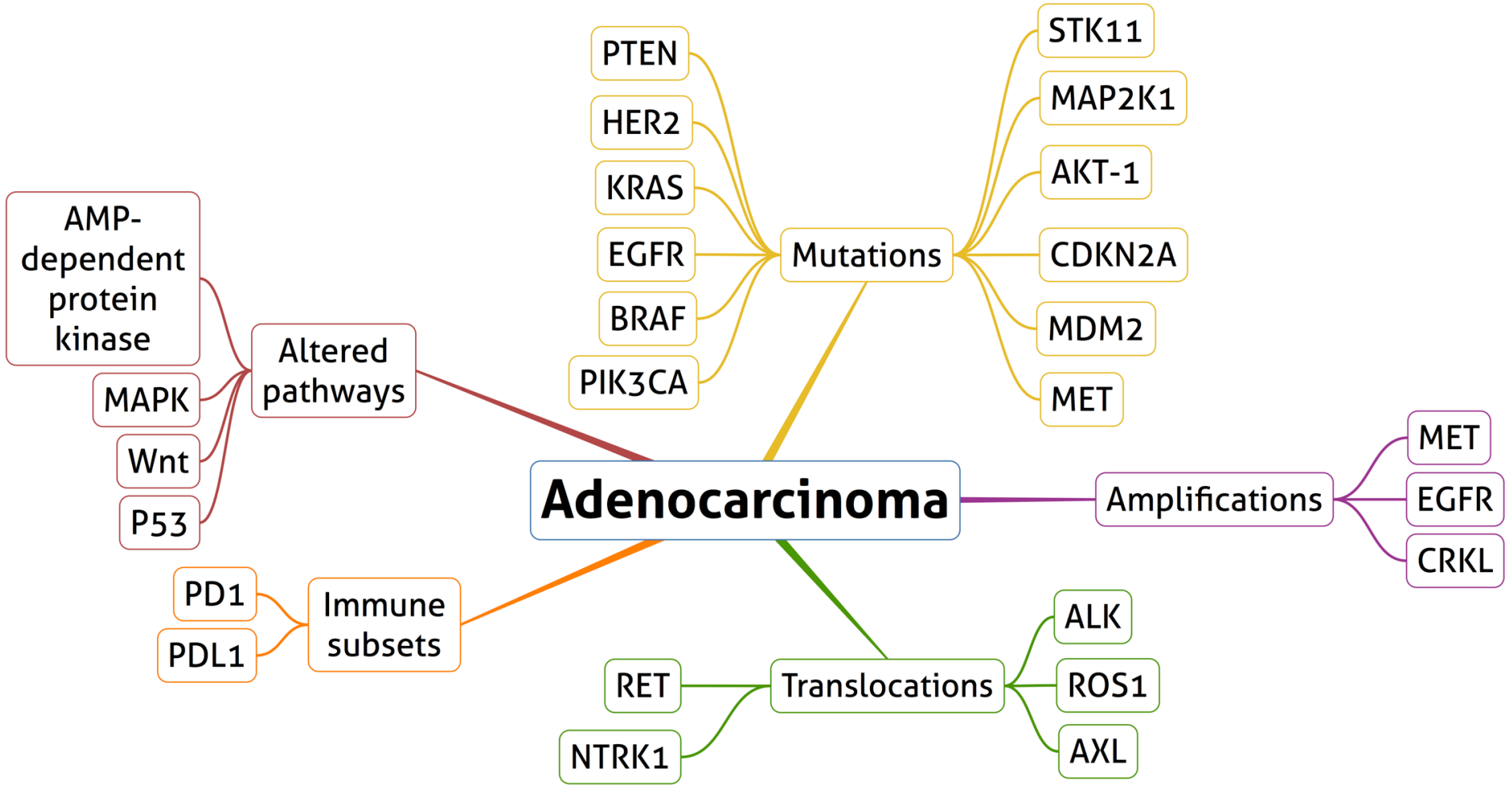
Brockley et al., Cancers, 2023

Clinical Applications of Liquid Biopsies



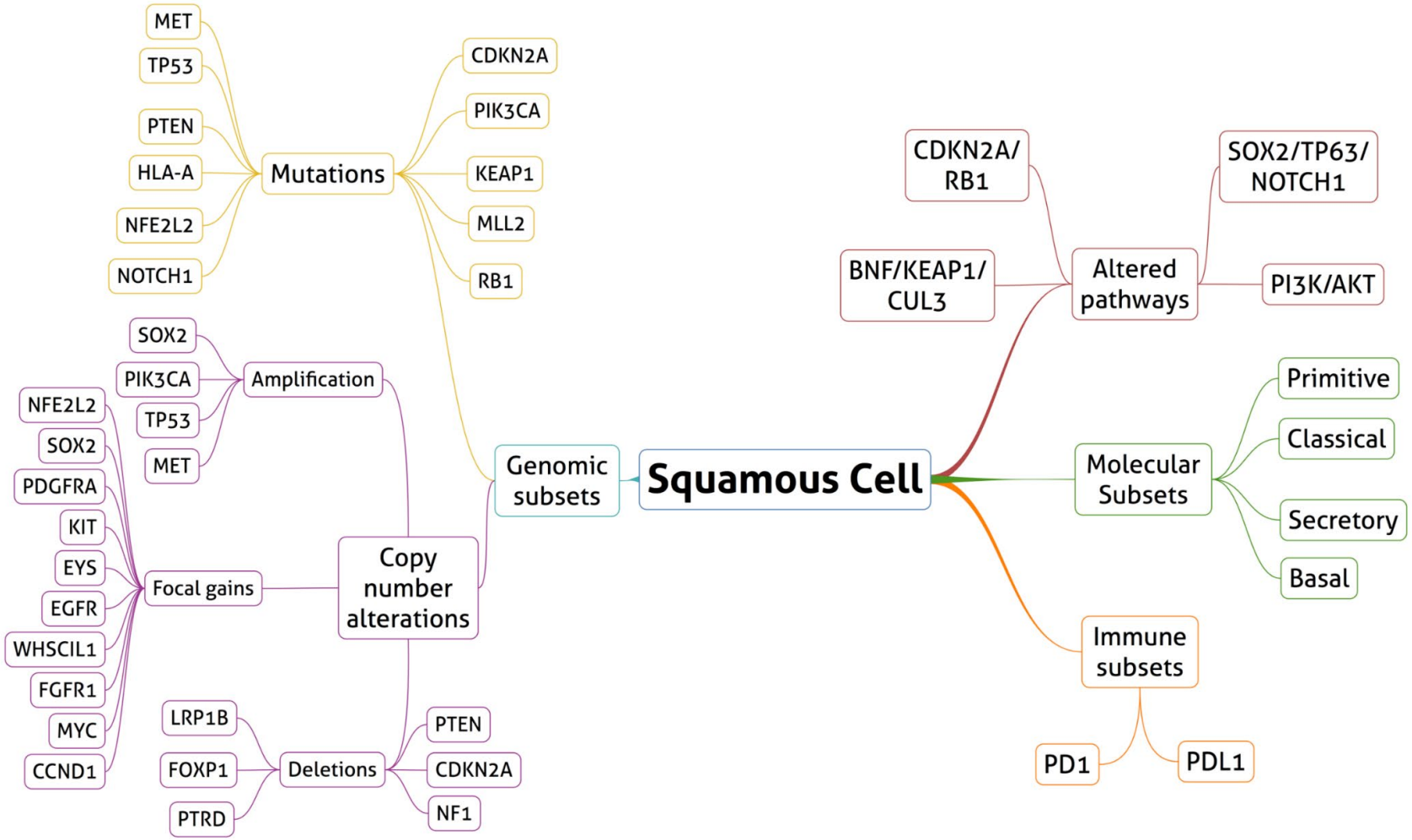
Caputo et al., Explor Target AntitumorTher., 2022

Lung Cancer- Adenocarcinoma Heterogeneity



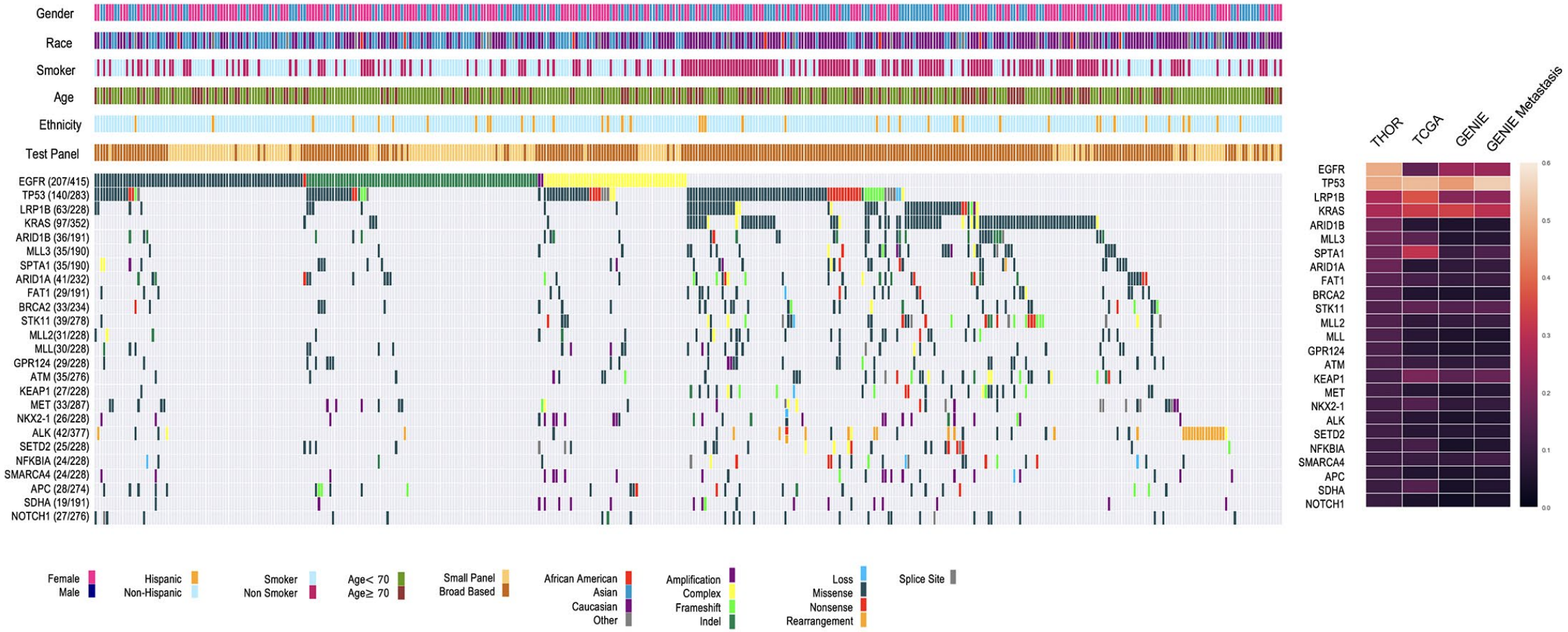
Hensing, Mambetsariev, Salgia; 2017; in Pass et al. IASLC Thoracic Oncology 2nd Ed.

Lung Cancer- Squamous Heterogeneity



Hensing, Mambetsariev, Salgia; 2017; in Pass et al. IASLC Thoracic Oncology 2nd Ed.

Lung Cancer- Heterogeneity



Mambetsariev et int. Salgia, PlosOne, 2020

When to consider genomic tumor testing for “NSCLC”

Initial Presentation

- Is there enough tissue for molecular testing?
- Is a biopsy required?
- Is there pleural fluid for potential biopsy?

Features of a particular patient/scenario to consider:

- Histology (Squamous cell carcinoma vs Non-Squamous)
  - If squamous, does it have adenocarcinoma features?
- Stage
  - Stage I-III vs Stage IV
- Age
  - Is the patient younger than 50 or older than 65
- Prior Testing/Treatment
  - Previous history of other cancer types
  - Previous molecular testing results (should you re-biopsy?)
  - Previous treatment for early-stage vs recurrence

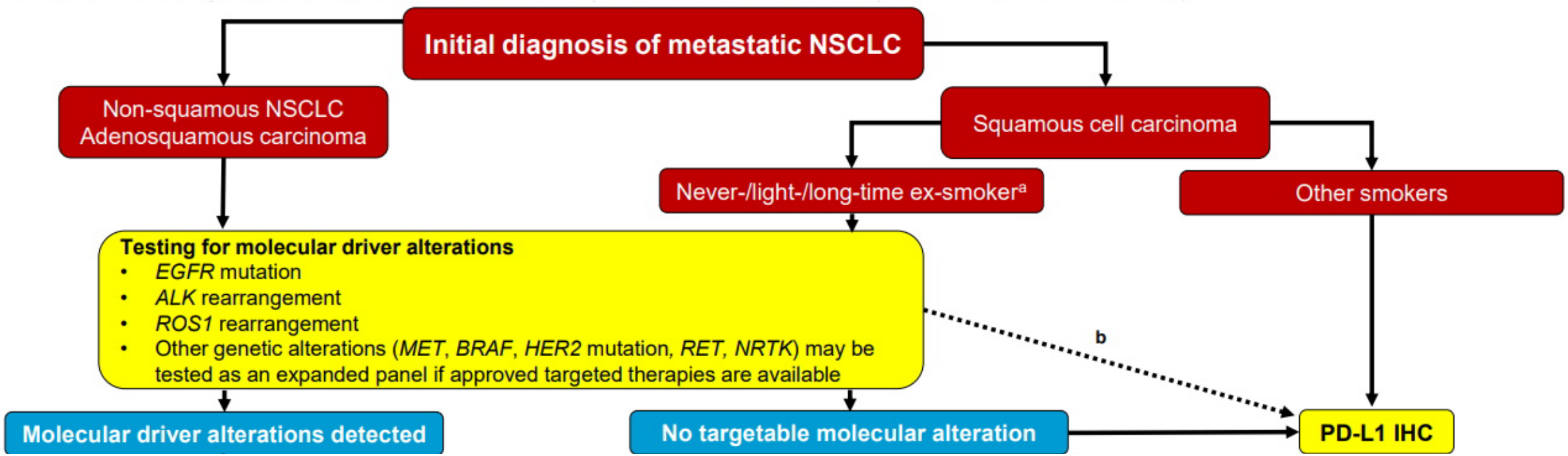
NSCLC Biomarker Testing Rates

Nonsquamous NSCLC	Decisions in Academic Setting (n = 51)	Decisions in Community Setting (n = 253)	Total # of Decisions (N = 304)
***ALK* Test Status**			
Awaiting test results	6	74	80
Did not order test	0	19	19
Negative	42	157	199
Positive	3	3	6
ALK testing rate, n (%)	51 (100)	234 (92)	285 (94)
***EGFR* Test Status**			
Awaiting test results	6	76	82
Did not order test	0	16	16
Negative/wild type	19	100	119
Non-sensitizing	7	27	34
Sensitizing	19	34	53
EGFR testing rate, n (%)	51 (100)	237 (94)	288 (95)
***ROS1* Test Status**			
Awaiting test results	6	72	78
Did not order test	0	37	37
Negative	43	142	185
Positive	2	2	4
ROS1 testing rate, n (%)	51 (100)[a]	216 (85)[a]	267 (88)
Nonsquamous and Squamous NSCLC	**Decisions in Academic Setting (n = 45)**	**Decisions in Community Setting (n = 282)**	**Total # of Decisions (N = 327)** [b]
PD-L1 Test Status			
Negative	15	57	72
Positive (≥ 50% TPS)	8	55	63
Positive (1%–49% TPS)	5	47	52
Did not order test	17	123	140
PD-L1 testing rate, n (%)	28 (62)	159 (56)	187 (57)

Reported Study	EGFR	ALK	ROS1	MET	RET	NTRK	BRAF	KRAS	PD-L1 Expression
Inal et al. [66]	62%	23%	N/A	N/A	N/A	N/A	N/A	43%	N/A
Gutierrez et al. [67]	69%	65%	25%	15%	14%	N/A	18%	34%	N/A
Gierman et al. [68]	54%	51%	43%	N/A	N/A	N/A	29%	N/A	N/A
Presley et al. [69]	100%	95%	~15%	~15%	~15%	~15%	~15%	~15%	~15%
Illei et al. [94]	N/A	53.1%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hussein et al. [95]	~60%	~50%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mason et al. [29]	94%	92%	85%	N/A	N/A	N/A	N/A	N/A	56%
Audibert et al. [105]	68%	67%	32%	6%	8%	0%	12%	0%	N/A
Khozin et al. [142]	64%	61%	N/A	N/A	N/A	N/A	N/A	N/A	8.3%
Nadler et al. 2018 [143]	37%	35%	N/A	N/A	N/A	N/A	N/A	N/A	1.2%
Nadler et al. 2019 [106]	35.5%	32.9%	5.7%	N/A	N/A	N/A	0.1%	N/A	5.7%

Mason et al., J Clin Pathw, 2018
Rajurkar et int. Salgia, JCM, 2020

Stage IV NSCLC Molecular Testing Algorithm by Histology



Chong-Kin et al., Respirology, 2020

Genomic Tumor Testing in Lung Cancer

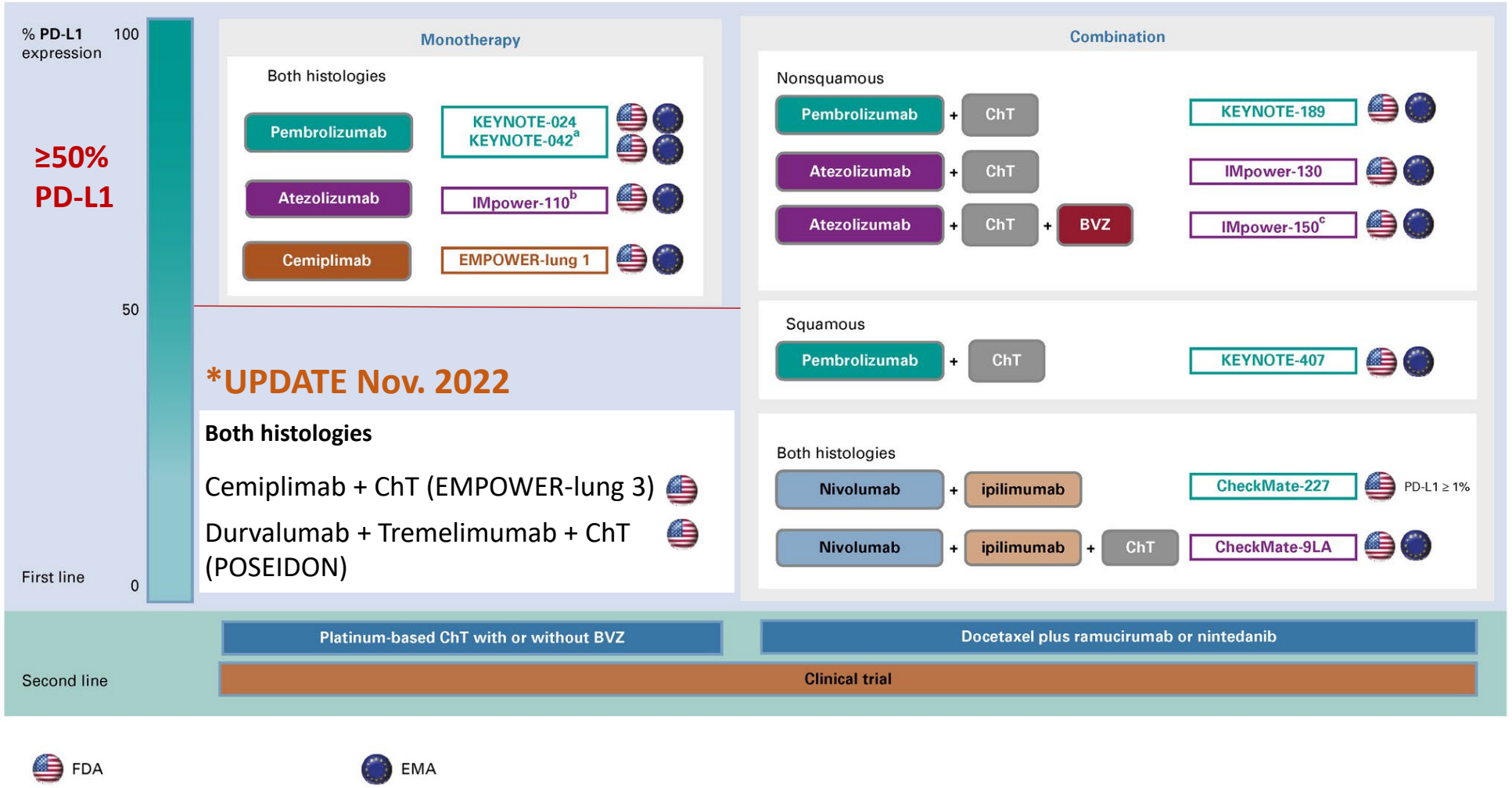
What to consider when choosing test type for these patients:

- Comprehensive panels tissue biopsy
  - HopeSeq
  - FoundationOne CDX
  - Tempus
  - CARIS
  - Neogenomics
- Liquid Biopsy
  - Blood
    - Guardant 360
    - FoundationOne Liquid CDX
    - Tempus
    - Neogenomics
  - Cerebrospinal Fluid
    - Biocept
- Specific markers (e.g. PDL-1)
  - Full NGS panel (EGFR, ALK, KRAS, MET, ROS1, BRAF, NTRK, RET, HER-2, and more with up to >450 genes)
  - IHC (PD-L1)
    - 22C3 (Pembrolizumab, Cemiplimab)
    - SP142 (Atezolizumab)
    - 28-8 (Nivolumab)
    - SP263 (Durvalumab)

Interpreting Biomarker Testing in Lung Cancer

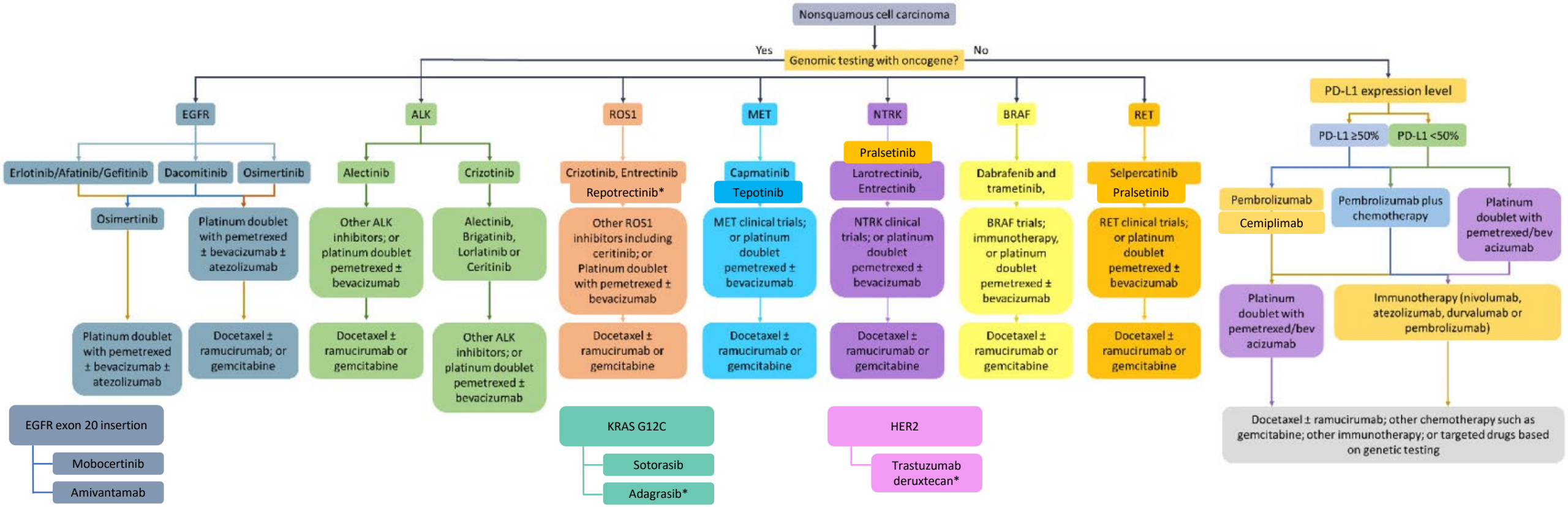
- What to consider when a patient has an actionable mutation?
  - EGFR, ALK, KRAS G12C, MET, BRAF V600E, RET, ROS1, NTRK fusion, HER2
  - Is there a rare subtype such as EGFR exon 20, exon 18, or MET fusion?
  - Are there any co-mutations such as KRAS-KEAP1-STK11 or EGFR-RB1-TP53?
- PD-L1 results
  - 0% PD-L1 negative
  - ≤1-49% PD-L1 positive
  - ≥50% PD-L1 positive (high expression)
  - Are there any mutations that may cause hyper-progression? (KRAS-KEAP1-STK11 or actionable mutations such as EGFR)
- Do any of the genomic results dispute the histologic diagnosis?
- Germline results:
  - BRCA-1 or BRCA-2 becoming more common in lung cancer
  - ATM, PARK2, TP53, EGFR and others

Immunotherapy: Stage IV NSCLC



Reck, Remon, and Hellmann; J. Clin. Oncol., 2022

Lung Cancer Targeted Therapeutic Strategies



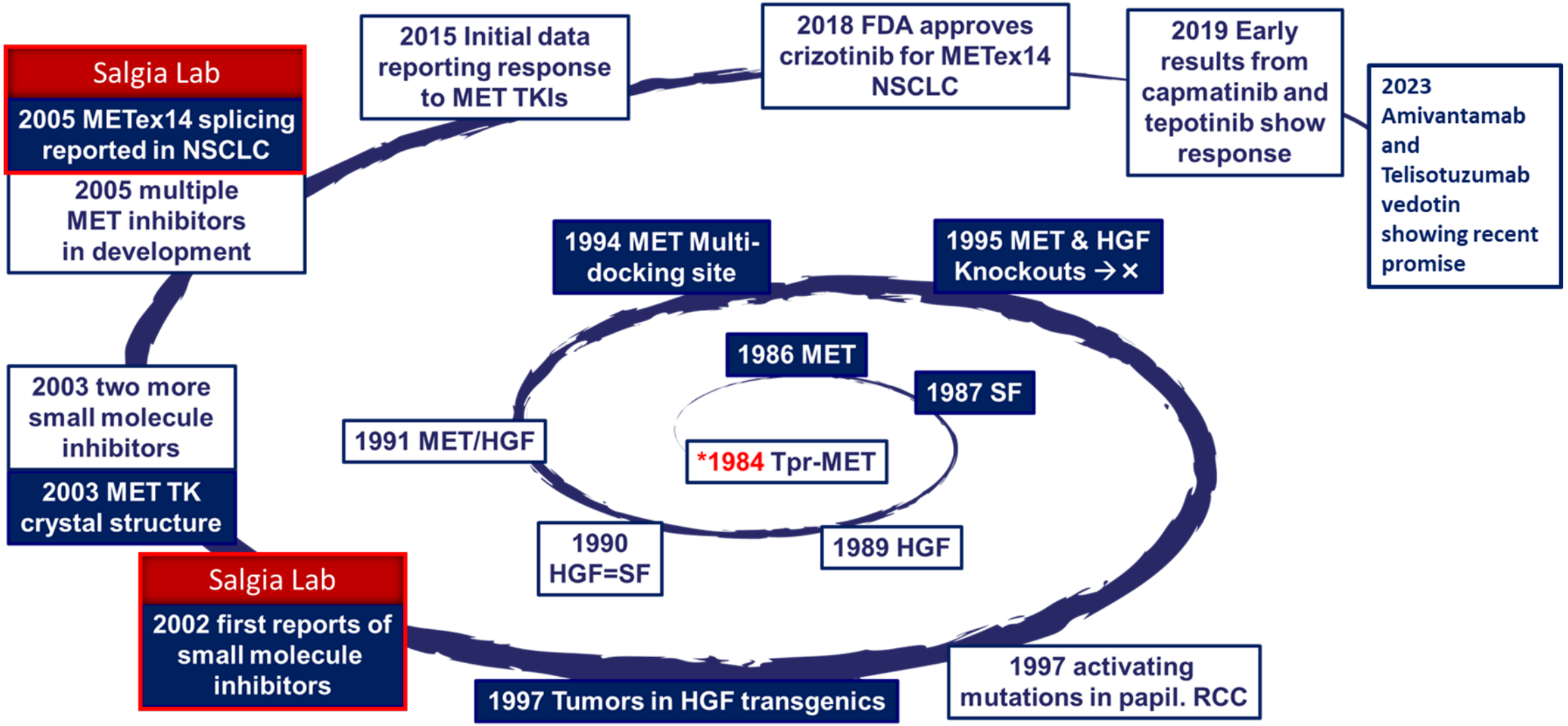
Targeted therapies

*Breakthrough Designation

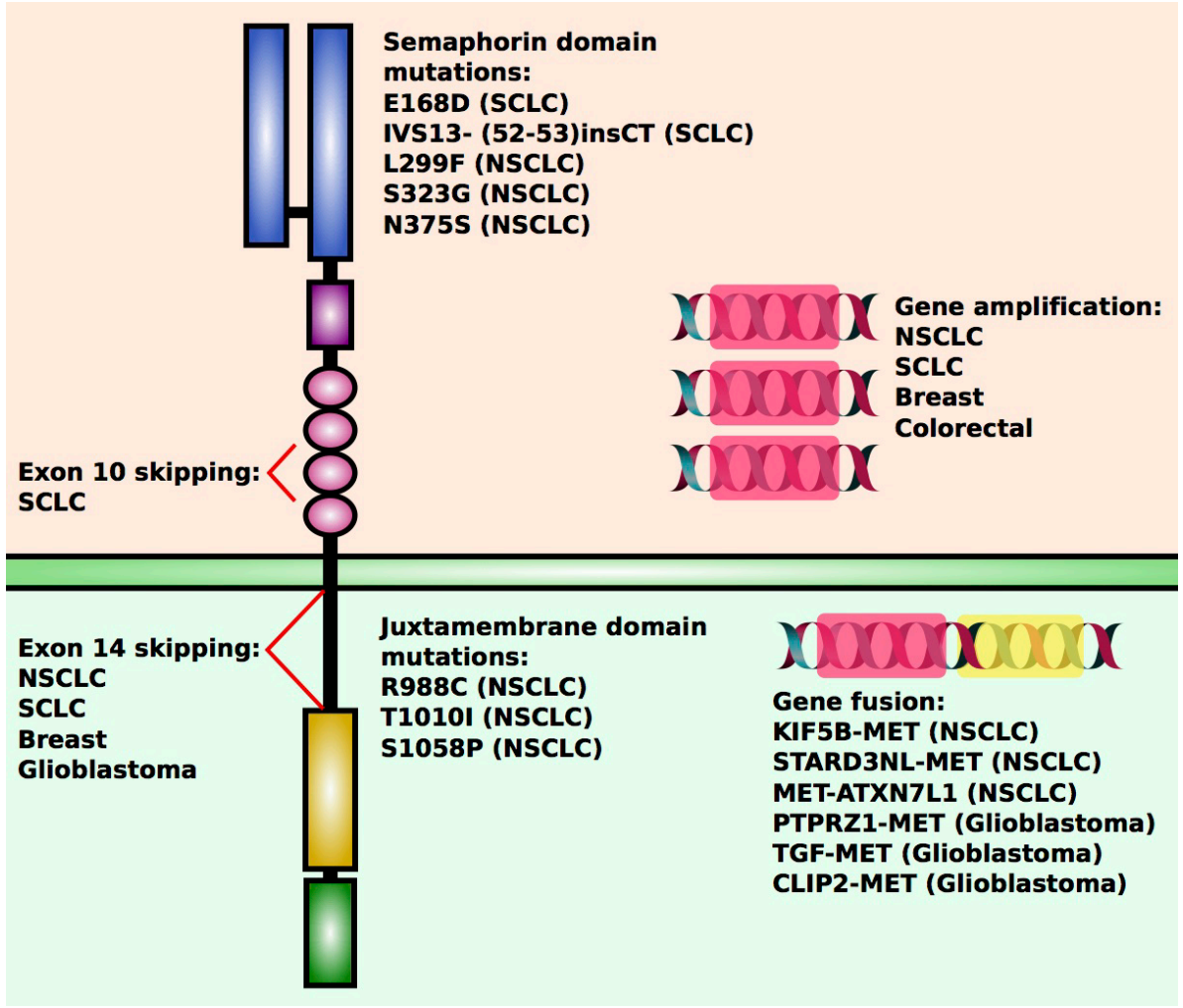
Immunotherapies

Rajurkar et int. Salgia, JCM, 2020 (Updated 2022)

Timeline of MET Discoveries

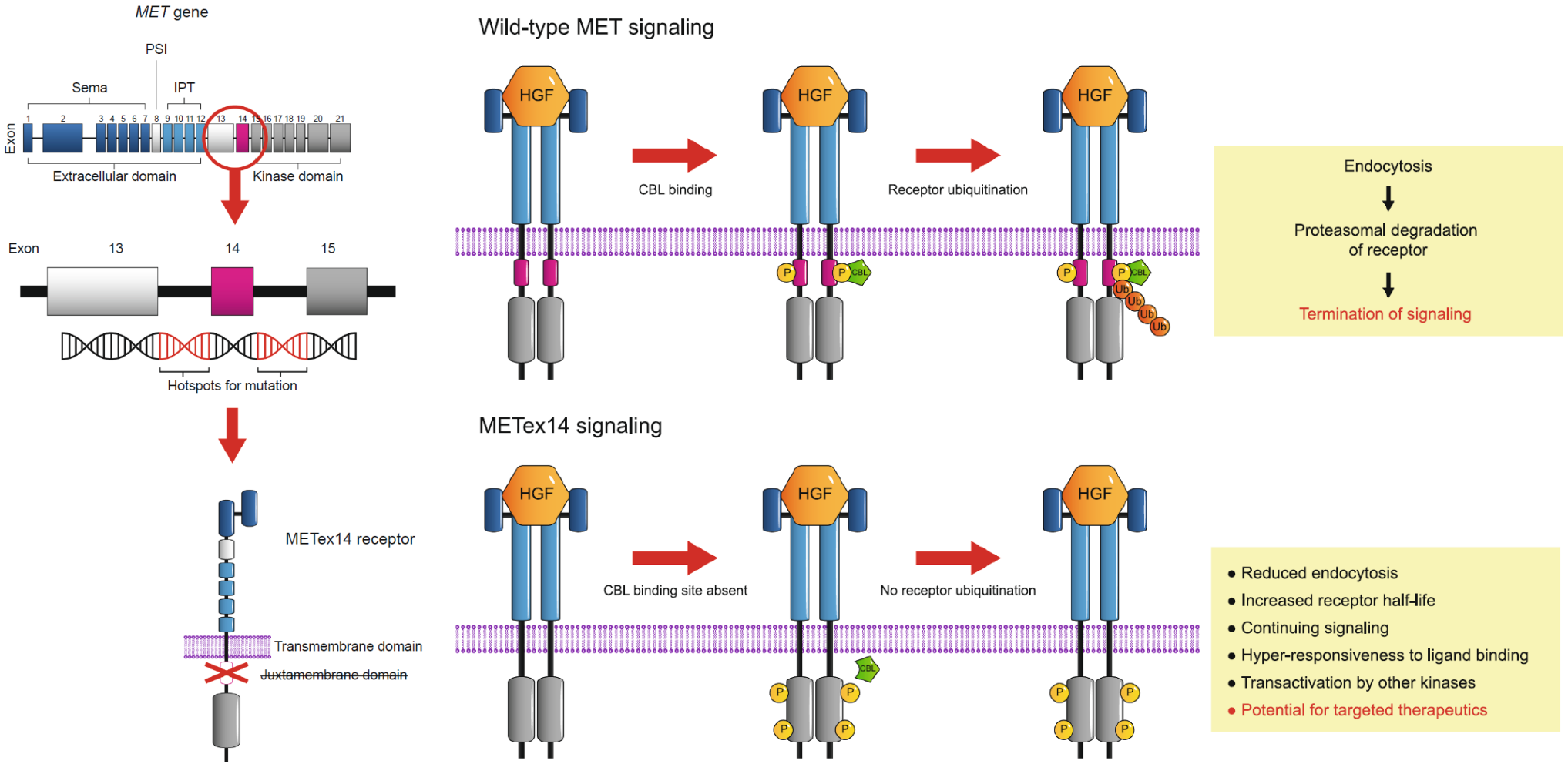


Genetic Alterations of MET Found in Solid Tumors



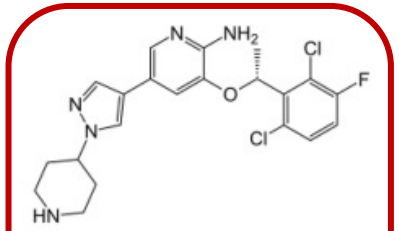
Malik, et int. Salgia, ACR 2020

MET Exon 14 Mutation and Downstream Signaling

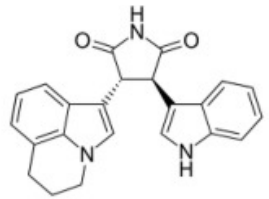


Salgia R., Sattler M., et al. Cancer Treatment Reviews, 2020

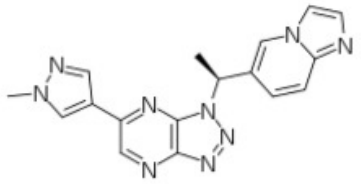
New Generation of Small-molecule MET Inhibitors



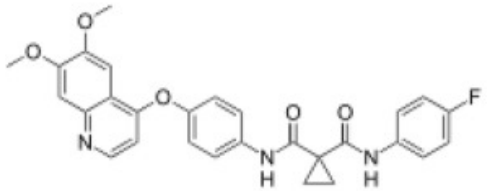
Crizotinib (PF-02341066)
- FDA-approved as an ALK inhibitor
- Inhibit MET, ALK, ROS1 and RON
- IC_{50} for MET: 0.0002 μM



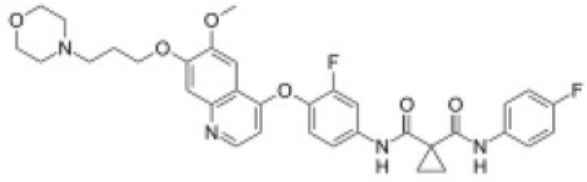
Tivantinib (ARQ197)
- Phase II combined with erlotinib in NSCLC
- Inhibit MET
- IC50 for MET: N/A



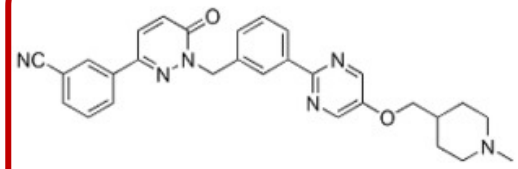
Savolitinib (HMPL-504; AZD6094)
- Phase II with NSCLC
- Inhibit MET
- IC_{50} for MET: 0.003 μM



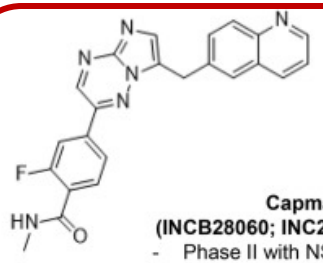
Cabozantinib (XL184, BMS907351)
- FDA-approved for renal and thyroid cancers
- Inhibit MET, VEGFR2, AXL and RET
- IC_{50} for MET: 0.0013 μM
- Phase II with NSCLC



Foretinib (XL880; EXEL-2880; GSK1363089; GSK089)
- Inhibit MET and VEGFR2
- IC_{50} for MET: 0.0004 μM
- Phase I in combination with erlotinib in NSCLC



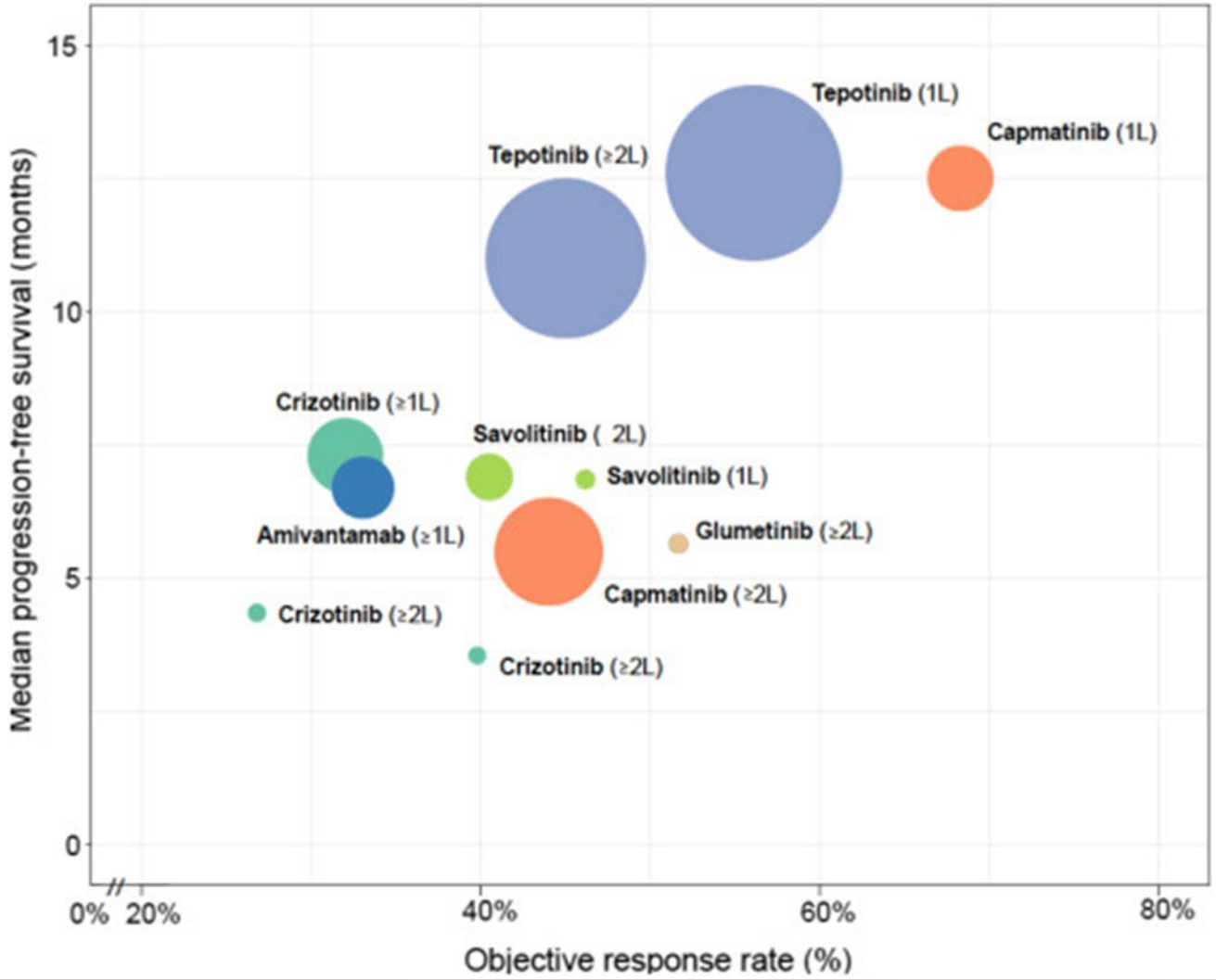
Tepotinib (EMD 214063)
- Phase II with MET-altered NSCLC
- Inhibit MET
- IC_{50} for MET: 0.001 μM



Capmatinib (INCB28060; INC280, NVP-INC280)
- Phase II with NSCLC
- Inhibit MET
- IC_{50} for MET: 0.00013 μM

Wang et al. J Hematol Oncol, 2019

Efficacy of MET Inhibitors



Remon et al., JCO, 2023

Case #1: MET

- 66-year-old male, never smoker, initially presented with dyspnea on exertion, and a cardiac MRI revealed biventricular masses consistent with metastatic disease.
- Additionally, CT showed a 5.7 cm RUL mass, subcentimeter pulmonary nodules, mediastinal and hilar lymphadenopathy, hepatic masses, bilateral adrenal nodules, and lytic lesions.
- Brain MRI showed multiple small sub-centimeter lesions.
- Liver biopsy confirmed stage IV lung adenocarcinoma (T3N3M1c) with PD-L1 70%, but as insufficient for molecular testing.

Roth et int. Salgia, Cold Spring Harb. Mol. Case Stud. 2020

Case #1: MET Cont.

- He started Carboplatin/Paclitaxel for two cycles with Bevacizumab for the second cycle and developed G3 fatigue and G3 neuropathy; therapy was switched to Pembrolizumab.
- NGS was performed on a LN EBUS and revealed MET exon 14 splice site mutation.
- He developed PD in the chest and enrolled in a clinical trial with Tepotinib.
- The time course of the disease in both the chest and brain can be seen in (**Figure 1**).
- Patient continues treatment with Tepotinib (currently on cycles 83-84).

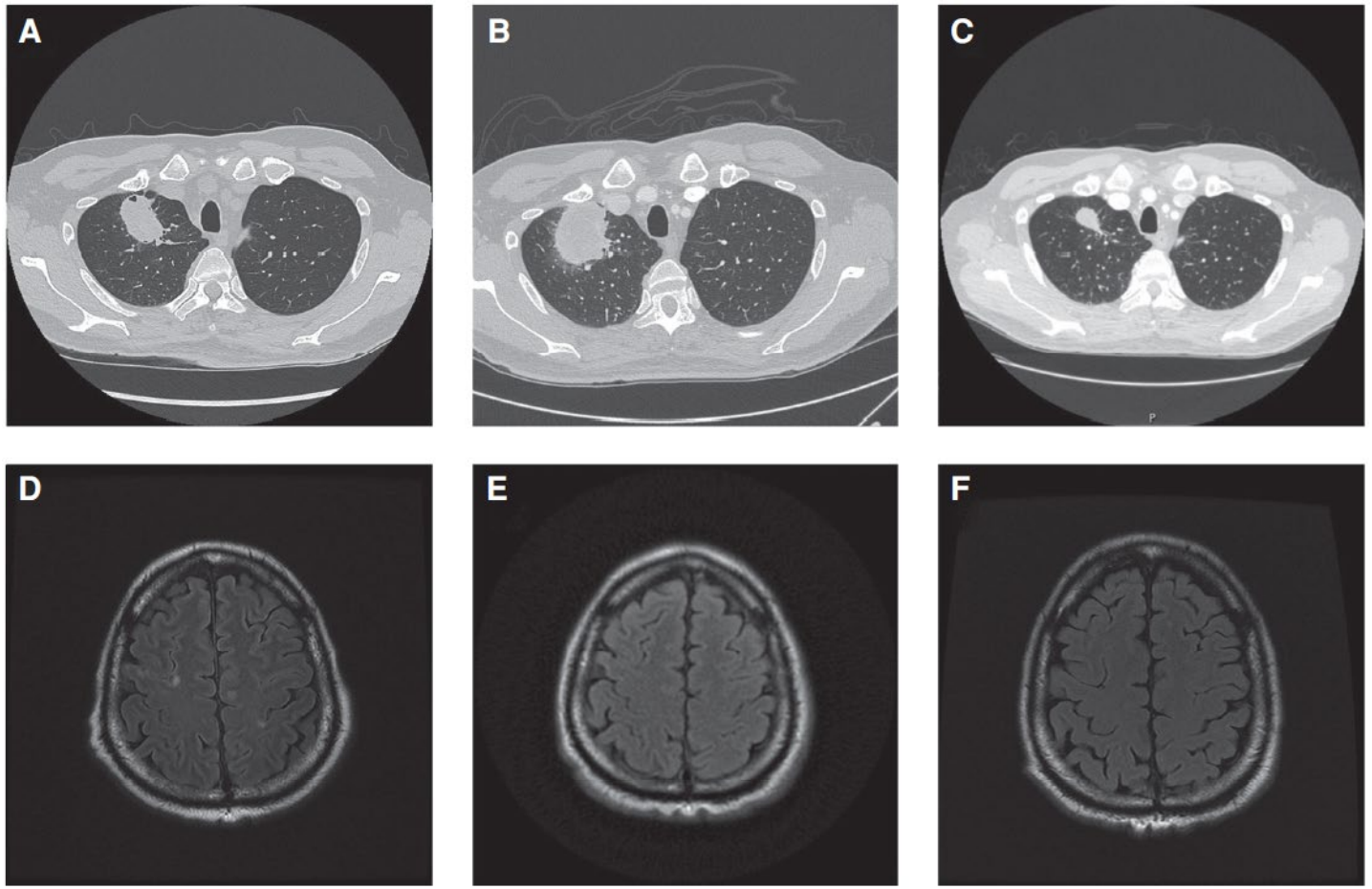
Roth et int. Salgia, Cold Spring Harb. Mol. Case Stud. 2020

Case #1: Treatment Response

Prior to treatment

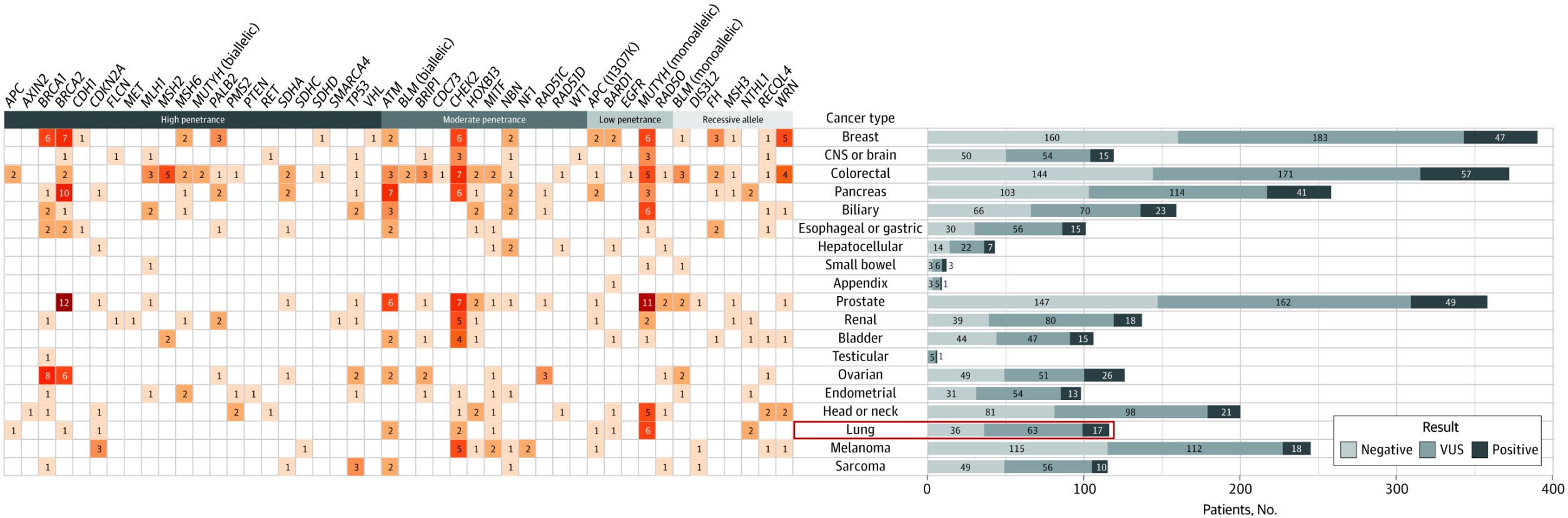
After 13 Cycles Pembrolizumab

After 40 Cycles Tepotinib



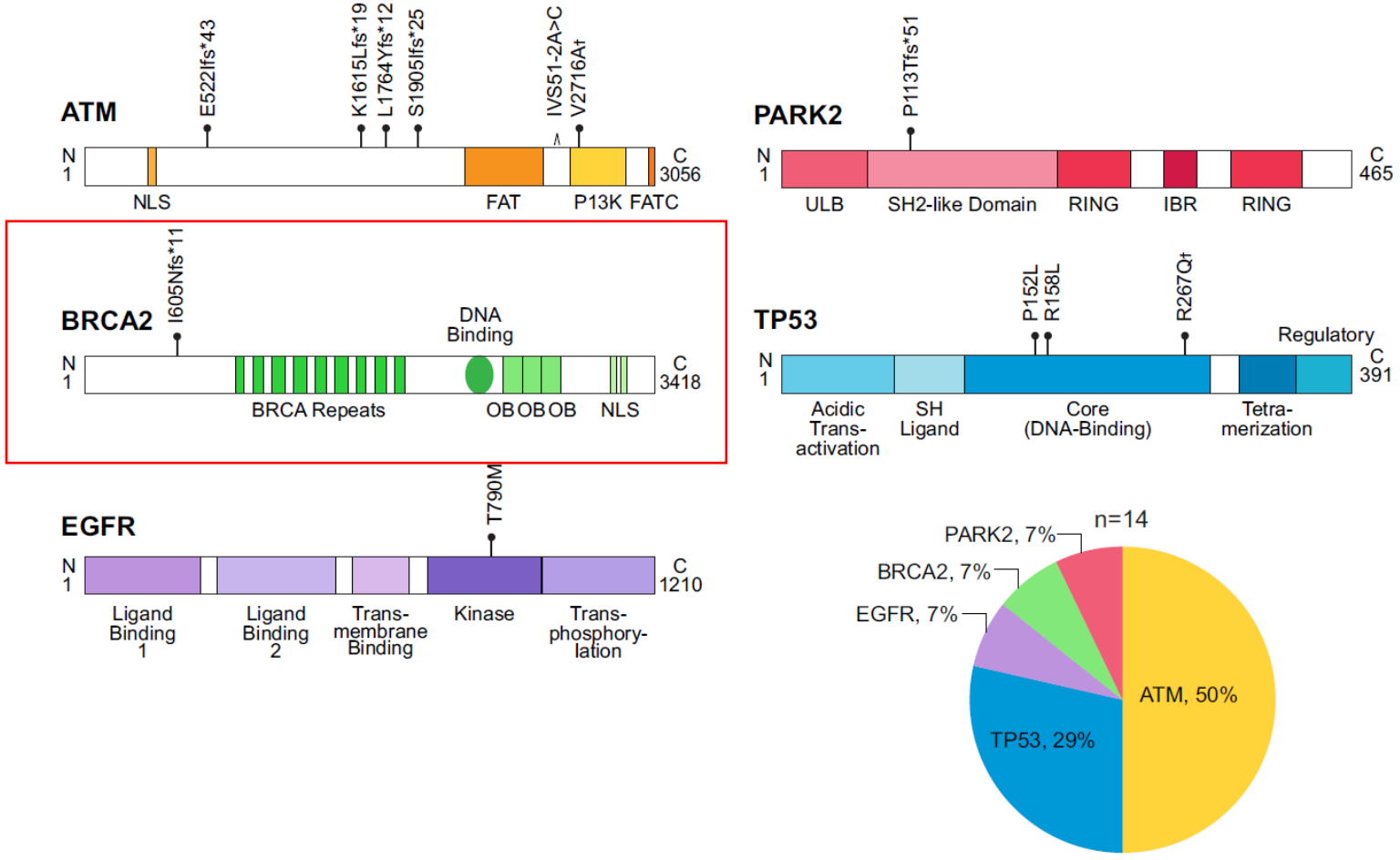
Roth et int. Salgia, Cold Spring Harb. Mol. Case Stud. 2020

Lung Cancer- Germline Mutations Prevalent



Samadder et al., JAMA Oncology, 2020

Germline Variants in Lung Adenocarcinoma Cases



Parry et al., Journal of Thoracic Oncology, 2017

COH-Universal Germline Testing on all patients

Groundbreaking study supports germline genetic testing for all cancer patients

In a study published in *JAMA Oncology*, Mayo Clinic and Invitae researchers provided genetic testing and counseling to patients as part of their standard cancer care.

The INTERCEPT study

- The largest known multicenter study of universal testing of patients with cancer
- Published in *JAMA Oncology*
- Includes 2,984 patients with a new or active cancer diagnosis, across a broad mix of solid tumor cancer stages and types

The study found:

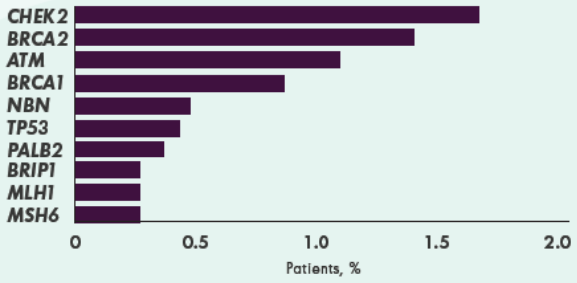
1 in 8 **patients with cancer had an inherited cancer-related genetic variant**

28% of patients with the highest risk cancer genes had **changes to medical management,** including chemotherapy and surgical decisions

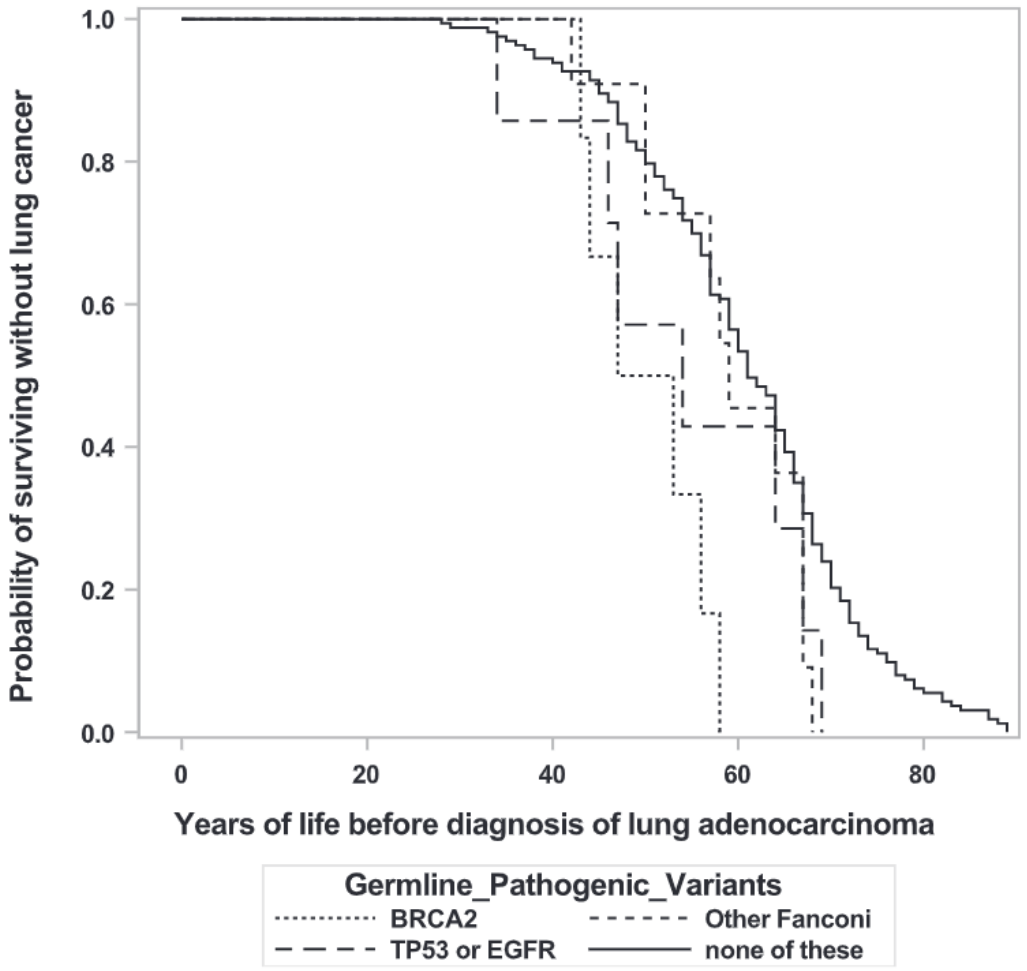
48%

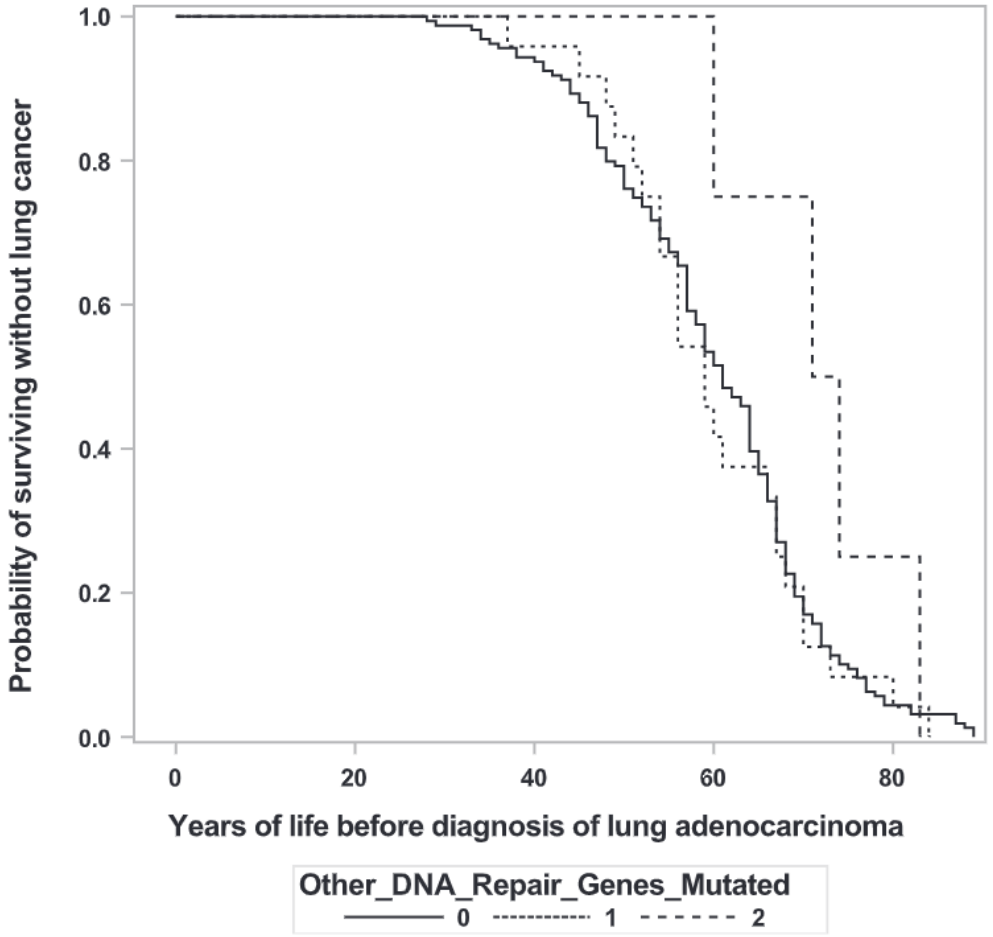
of **patients with inherited variants** were missed by existing testing guidelines

Most common pathogenic and likely pathogenic variants in high and moderate risk genes:



Lung Cancer- Germline Mutations Affect Survival





Reckamp et int. Salgia, Weitzel, Cancer, 2021

Case #2: Lung Cancer BRCA2

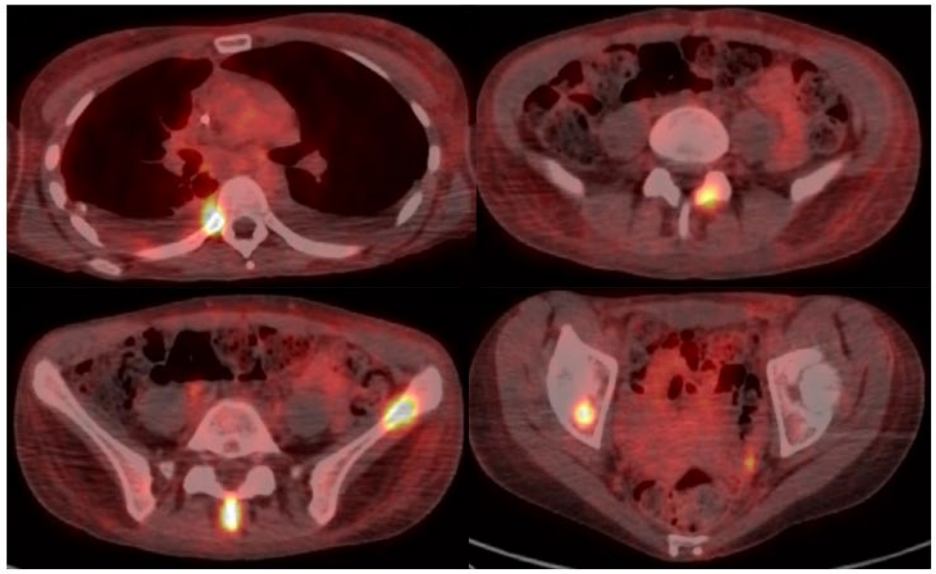
- 26-year-old female, no tobacco exposure or significant past medical history, initially presented with dyspnea.
- CTA of the chest demonstrated a RUL mass with mediastinal involvement creating superior vena cava syndrome along with associated pulmonary embolisms and a large right sided pleural effusion secondary to complete right bronchial tree collapse (Figure 1).
- Pleural effusion and biopsy revealed poorly differentiated lung adenocarcinoma.
- MRI brain demonstrated greater than 20 supratentorial and infratentorial lesions with the largest being 1.1 cm.
- PETCT demonstrated innumerable bilateral pulmonary micronodules, multiple osseous lesions including the right seventh rib, spine, sacrum, and left iliac wing (Figure 3).
- Clinically staged as IVB (T3N2M1c) primary lung adenocarcinoma.

Waddington et int. Salgia, Clinical Lung Cancer, 2021

Case #2: Work Up Imaging

Figure 1 Computed tomography (CT) angiography of the chest demonstrates a right upper lobe mass with mediastinal involvement creating superior vena cava (SVC) syndrome along with associated pulmonary embolisms and a large right sided pleural effusion secondary to complete right bronchial tree collapse.

Figure 3 PET-CT demonstrates innumerable bilateral pulmonary micronodules, multiple osseous lesions including the right seventh rib, spine, sacrum, and left iliac wing.



Waddington et int. Salgia, Clinical Lung Cancer, 2021

Case #2: Molecular Findings

- NeoGenomics genetic testing was negative for EGFR, ALK, and ROS1 while PD-L1 (22C3) testing demonstrated high expression with a tumor proportion score of 90%.
- Ashion GEM ExTra with DNA and RNA sequencing was notable for BRCA2 S497∗, TMB: Low at 4 muts/Mb and MSI: Stable.
- Liquid biopsy utilizing Guardant360 detected BRCA2 S497∗ with 51.6% of cfDNA.
- Germline BRCA1/2 analysis with CustomNext-Cancer was positive for the pathogenic mutation BRCA2 S497∗ (Table 1).
    - Patient's Mother (aged 47) and maternal half-brother (aged 21) tested positive for the BRCA2 mutation.

Table 1 The Patient's Germline Mutation in the BRCA2 Gene

Gene	Chromosome	HGVS DNA Reference	HGVS Protein Reference	Variant Type	Predicted Effect	dbSNP/ dbVar ID	Genotype (Heterogous or Homozygous	ClinVarID
BRCA2	13	NM_000059.3 (BRCA2): c.1490C>G (p.Ser497Ter)	NP_000050.2: p.Ser497Ter	Nonsense, stop-gain	Premature truncation	nsv4449760	Heterozygous	RCV000774812.3

Waddington et int. Salgia, Clinical Lung Cancer, 2021

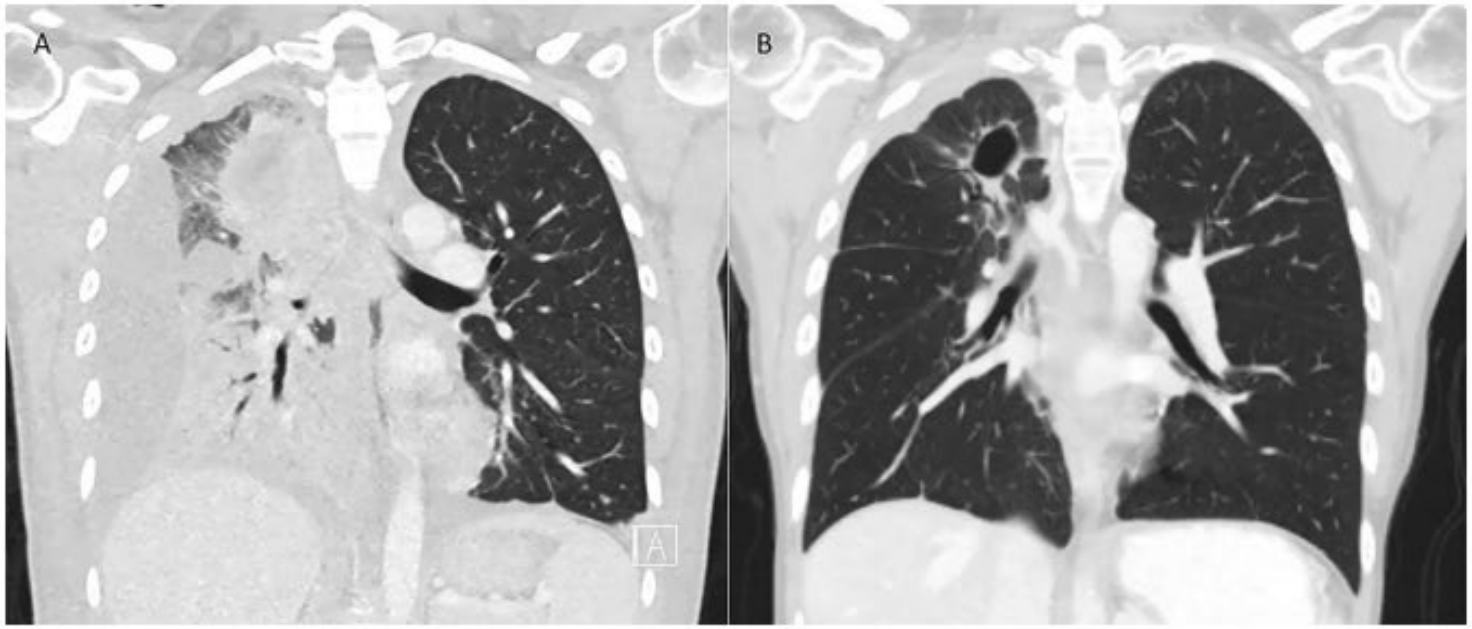
Case #2: Treatment

- Received one cycle of inpatient Carboplatin/Pemetrexed.
- Palliative radiation to her right lung and mediastinum with a total dose of 30 Gy delivered in 10 fractions along with WBRT reaching a total dose of 30 Gy over 10 fractions.
- Initiated combination Carboplatin (AUC 5)/Pemetrexed (500 mg/m2)/Pembrolizumab (200 mg) every 3 weeks for 5 cycles.
- Olaparib (150 mg, BID) was initiated with Pembrolizumab (200 mg), now every 6 weeks, for maintenance therapy (Figure 2).
- Patient continues therapy and is clinically and radiologically stable.

Waddington et int. Salgia, Clinical Lung Cancer, 2021

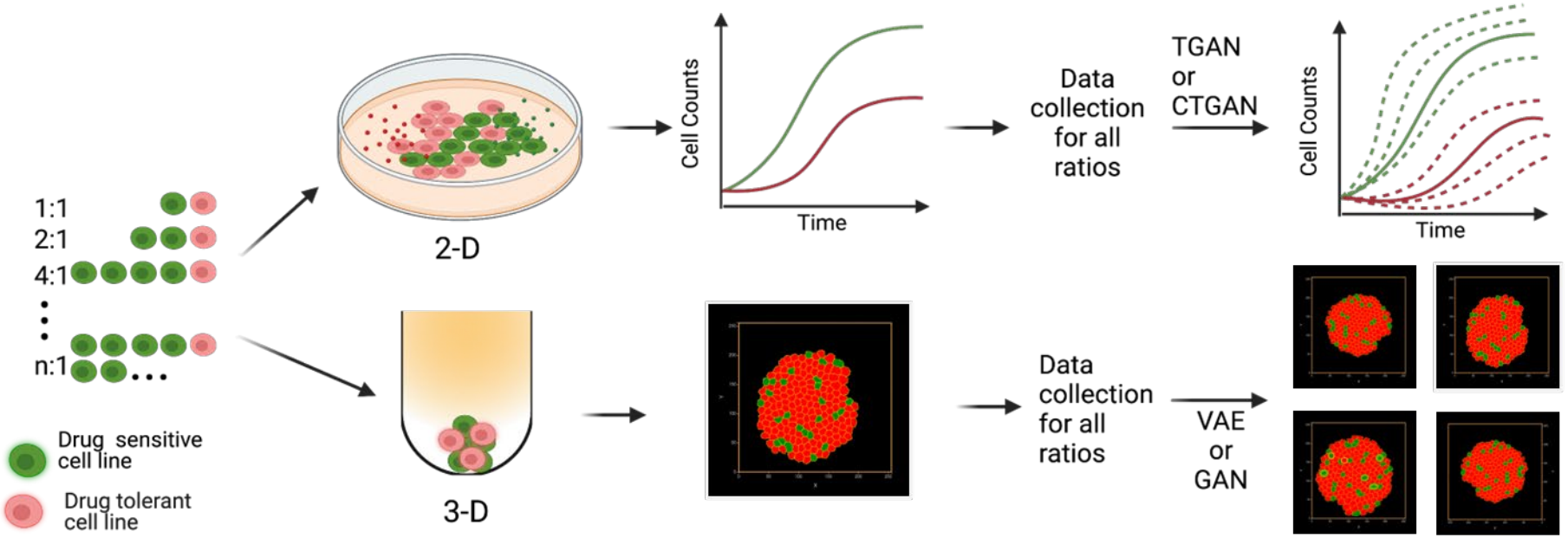
Case #2: Treatment Response

Figure 2 High resolution CT of the chest notes significant mediastinal adenopathy, bilateral pleural effusions and diffuse pulmonary nodules with the largest being in the posterior subsegment of the right upper lobe before (A) and after (B) treatment with chemotherapy/immunotherapy and olaparib.



Waddington et int. Salgia, Clinical Lung Cancer, 2021

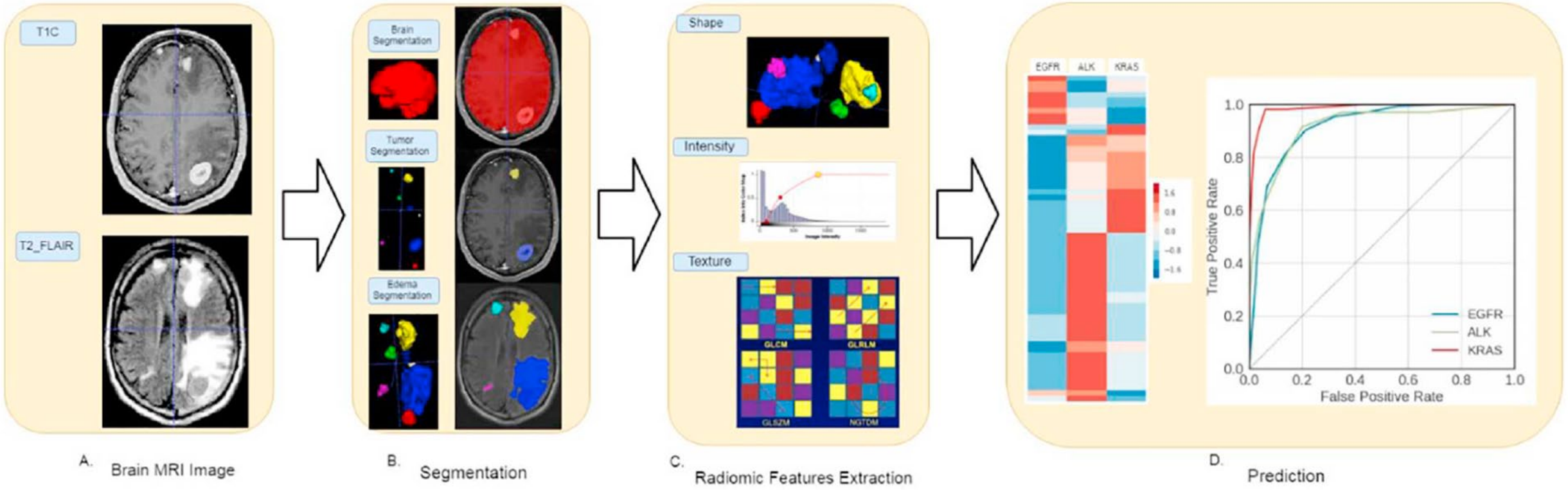
AI in Pre-clinical Research: Synthetic Tabular and Image Data Generated Using Deep Learning Algorithms (TGAN/CTGAN, VAE/GAN) Data



TGAN – Tabular Generative Adversarial Networks
CTGAN – Conditional Tabular Generative Adversarial Networks
VAE - Variational Autoencoders
GAN - Generative Adversarial Networks

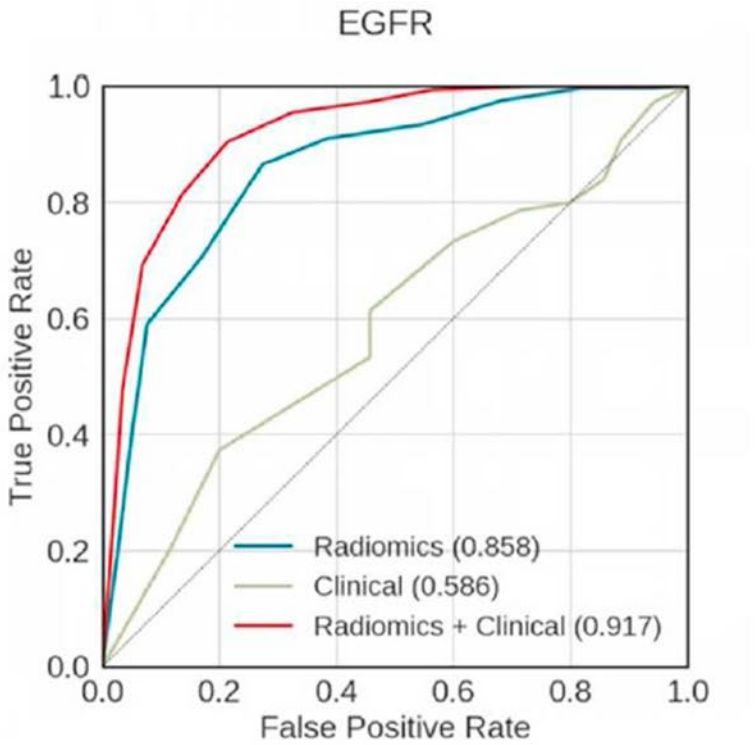
Achuthan et int. Salgia, J. Biosci, 2022

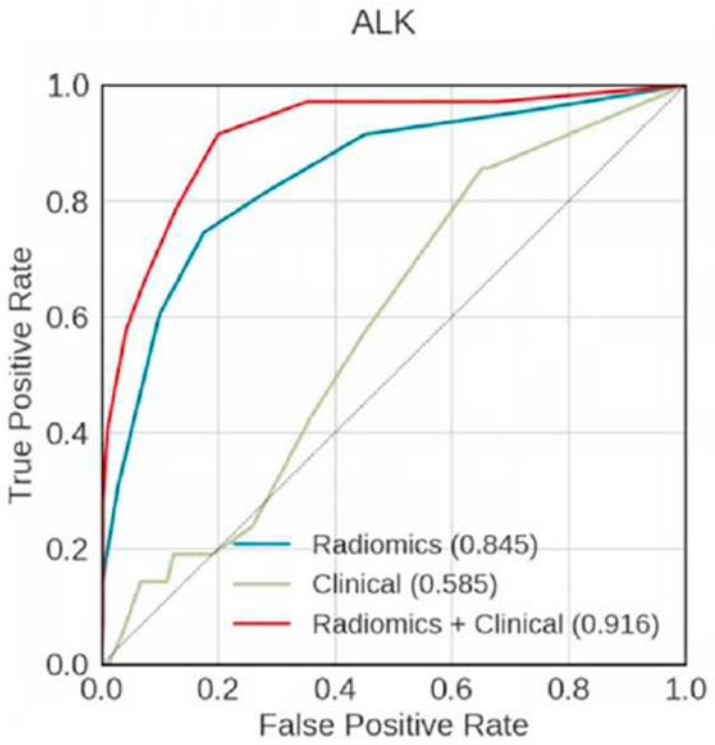
AI in Clinical Research: Predicting Mutational Status from MRI AI Models of Brain Metastases

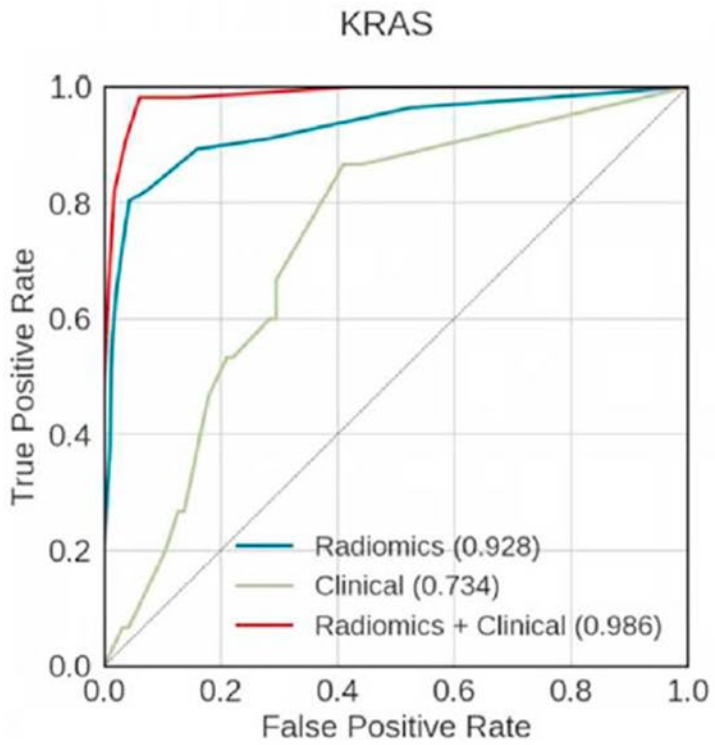


Chen et int. Salgia, Frontiers Oncology, 2021
Chen et int. Salgia, Magnetic Reason Imaging, 2020

AI in Clinical Research: Predicting Mutational Status from MRI AI Models of Brain Metastases



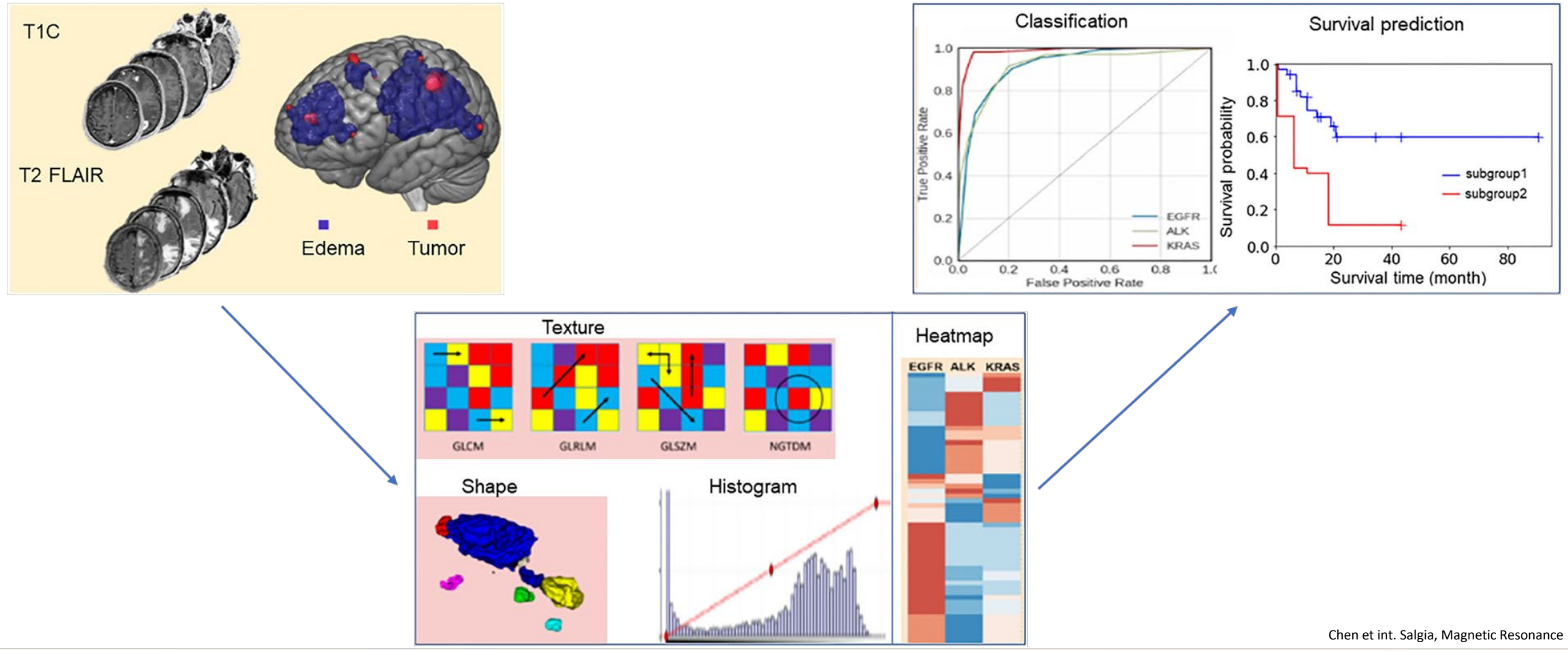




Chen et int. Salgia, Frontiers Oncology, 2021
Chen et int. Salgia, Magnetic Reason Imaging, 2020

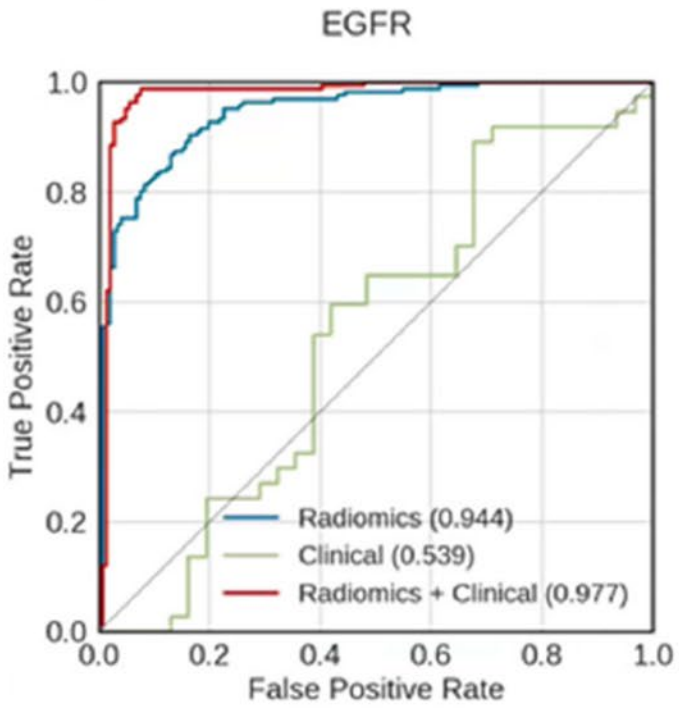
AI in Clinical Research: Predicting Survival from MRI AI Models of Brain Metastases

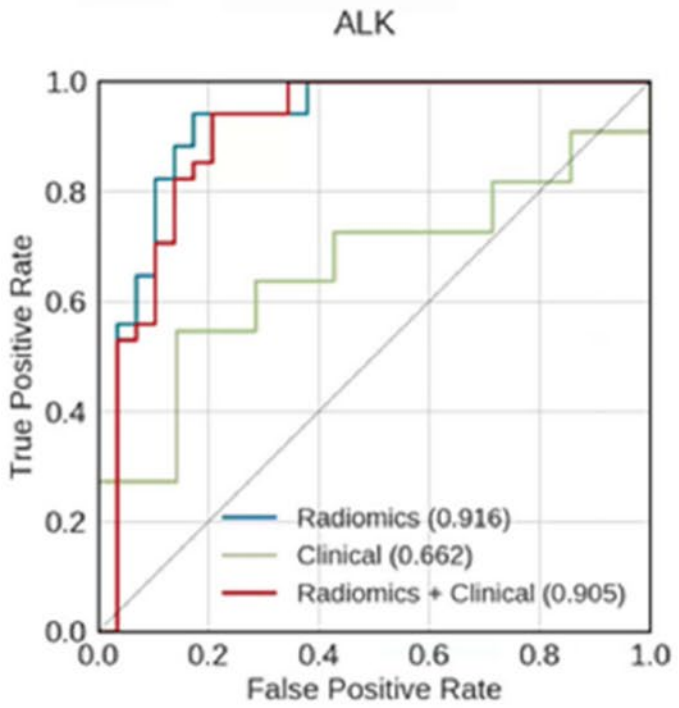
Schema for brain tumor segmentation, radiomic feature extraction, and predictive modeling

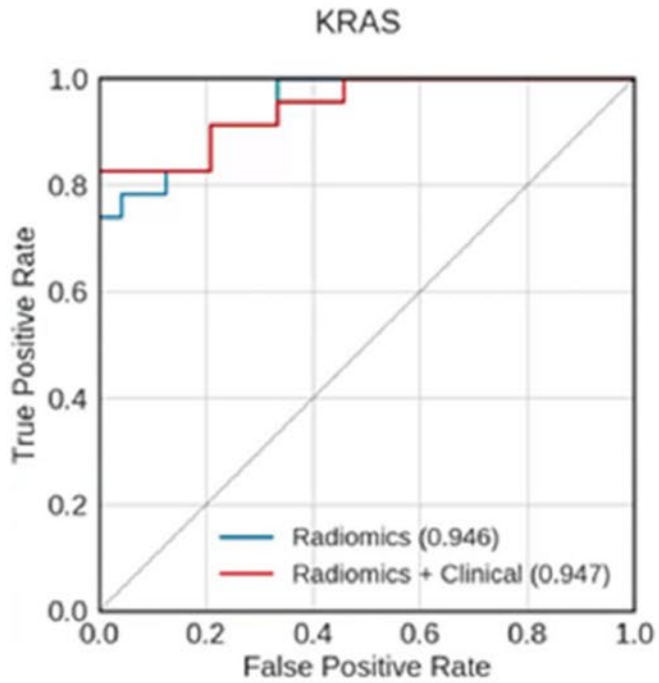


Chen et int. Salgia, Magnetic Resonance Imaging, 2021

AI in Clinical Research: Predicting Survival from MRI AI Models of Brain Metastases



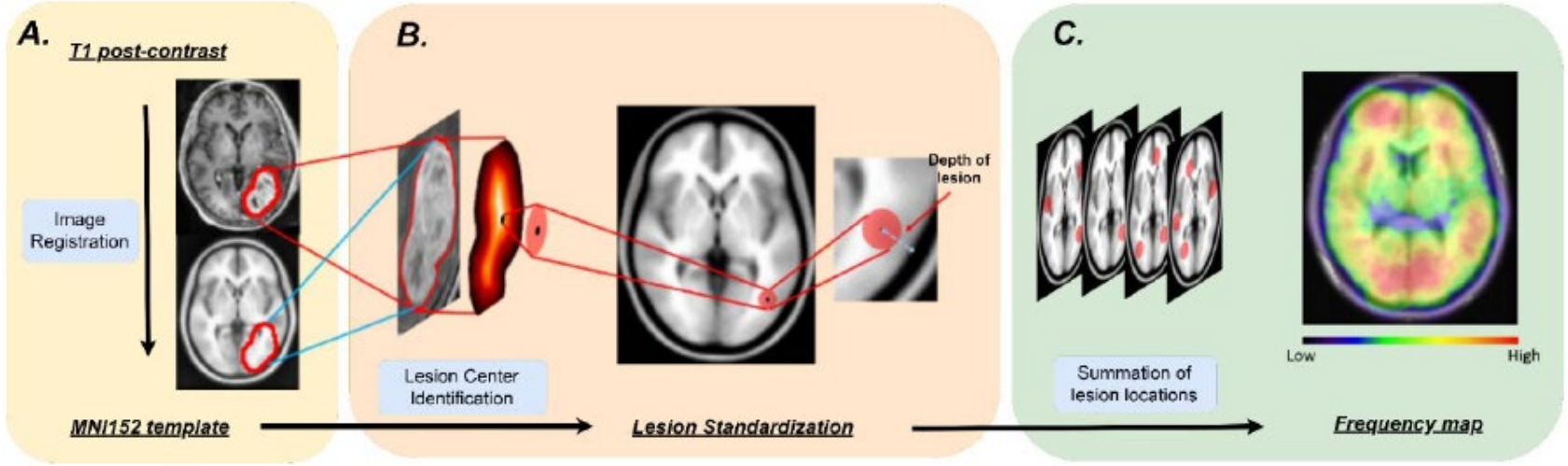




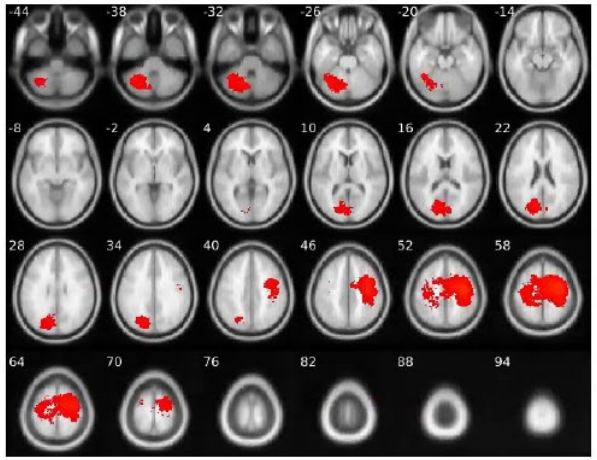
Mutation	Accuracy	AUC*	Sensitivity	Specificity
EGFR	94.90%	0.977	96.00%	94.00%
ALK	84.10%	0.905	88.00%	81.00%
KRAS	83.00%	0.947	83.00%	83.00%

Chen et int. Salgia, Magnetic Resonance Imaging, 2021

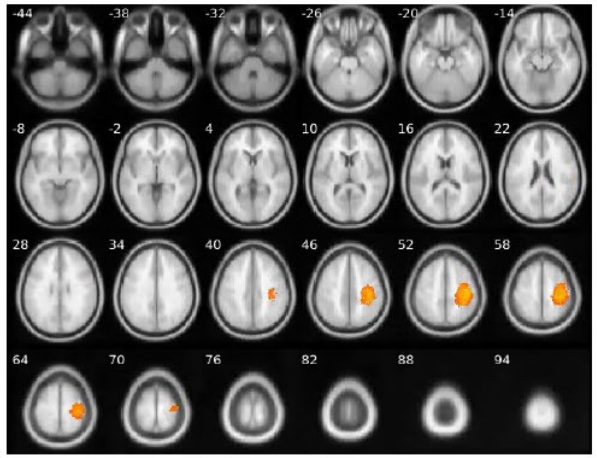
AI in Clinical Research: Predicting Distribution of Brain Metastases Based on Mutation Status from MRI AI Models



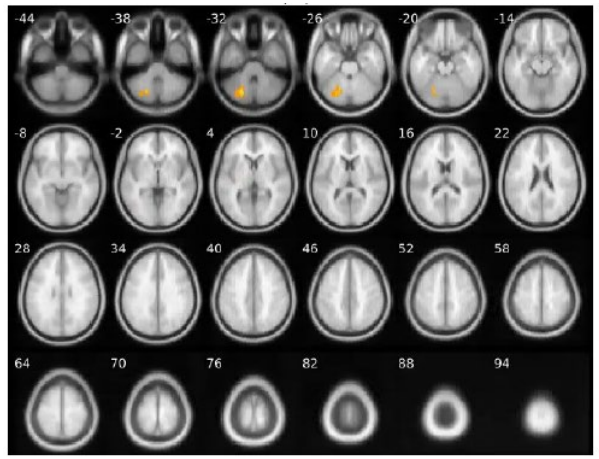
EGFR

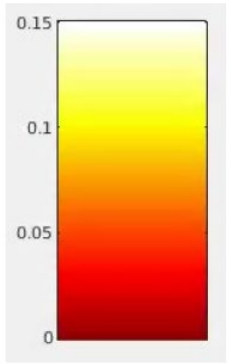


ALK



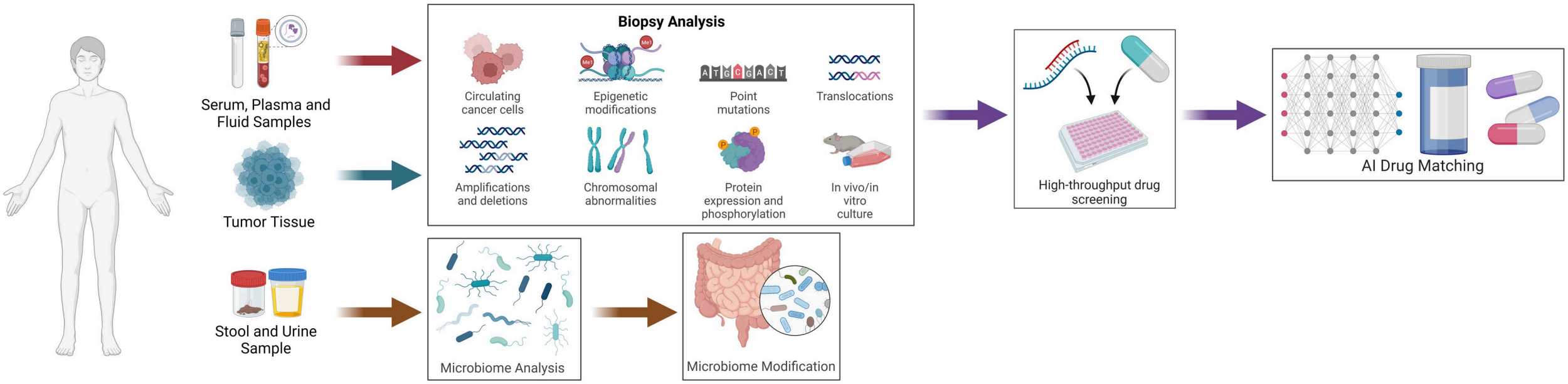
KRAS





Chen et int. Salgia, Brain Sci., 2023

Future of Precision Medicine



Mambetsariev, Fricke, et int. Salgia, JCM, 2023

Summary

- Next-generation Sequencing is necessary in patient workup and follow up care
- Precision Medicine relies on timely access to NGS testing and appropriate therapeutic initiation if available
- Genomic and Germline alterations have uncovered therapeutic options for more and more patients
- Artificial intelligence can enhance our understanding of Precision Medicine and clinical decision making
- More therapeutic research and breakthroughs necessary to achieve Personalized Medicine

Acknowledgment

City of Hope
Department of Medical Oncology
and Therapeutics Research