NATIONAL LUNG CANCER ROUNDTABLE

American Cancer Society®

Project ECHO®

Addressing Lung Cancer Biomarker Testing Through Project ECHO: 2022-2023 Expansion

Session 7
Biomarker-Driven Precision Medicine: Opportunities & Challenges

ACS/NLCRT Lung Cancer Biomarker Testing Project ECHO

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PLEASE WELCOME TODAY'S FACILITATIVE PARTNER

TODAY'S SESSION WILL BE

FACILITATED BY

DR. JHANELLE GRAY

DEPARTMENT CHAIR

&

PROGRAM LEAD

THORACIC ONCOLOGY

CO-LEAD MOLECULAR

MEDICINE PROGRAM

Jhanelle Gray, MD

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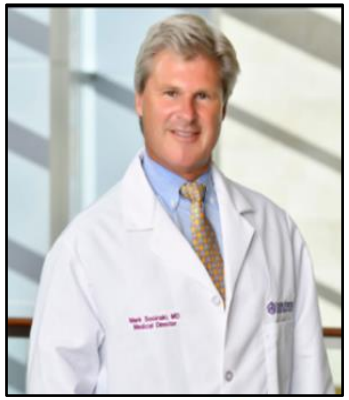
THANK YOU TO OUR FLORIDA FACULTY

Jhanelle E. Gray, MD

MOFFITT CANCER CENTER

*Facilitative Partner

Mark Socinski, MD



AdventHealth

Rami Manochakian, M.D

MAYO CLINIC

Luis Raez, MD

Memorial Healthcare System

Michael Diaz, MD

FLORIDA CANCER SPECIALISTS & Research Institute

Estelamari Rodriguez, MD

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

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Today's Agenda

Agenda Preview & Introductions (10 min)

Didactic Presentation: Dr. Estelamari Rodriguez
Biomarker-Driven Precision Medicine: Opportunities & Challenges (15 min)

Case Presentation: Dr. Samuel Kareff (10 min)

Case Based Discussion & Sharing: (20 min)

Post-Session Poll & Wrap Up (5 min)

This ACS/NLCRT Lung Cancer Biomarker Testing ECHO series is made possible by funding provided by:

Additional thanks to Foundation Medicine

MEET OUR FLORIDA ACS ECHO TEAM

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DIDACTIC PRESENTATION

Biomarker-Driven Precision Medicine: Opportunities & Challenges

Estelamari Rodriguez, MD, MPH
Clinical Research Lead Thoracic Oncology
Associate Director Community Outreach
Sylvester Comprehensive Cancer Center
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Twitter: @Latinamd

SYLVESTER COMPREHENSIVE CANCER CENTER
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The aim of Precision Medicine is to tailor treatment regimens to molecular drivers

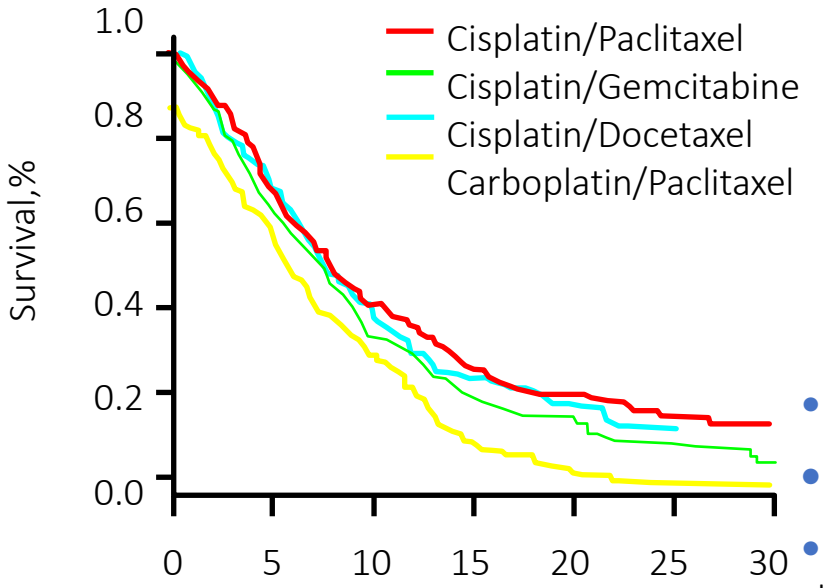
*Independent of histology

*Tumor Agnostic

*The N-of-1

How It Started

ECOG 1594



- **N=1155,**
- **ORR 19%**
- 1 yr survival plateau at about 35-40%
- (MS 7.9mos)
- No clear efficacy benefit

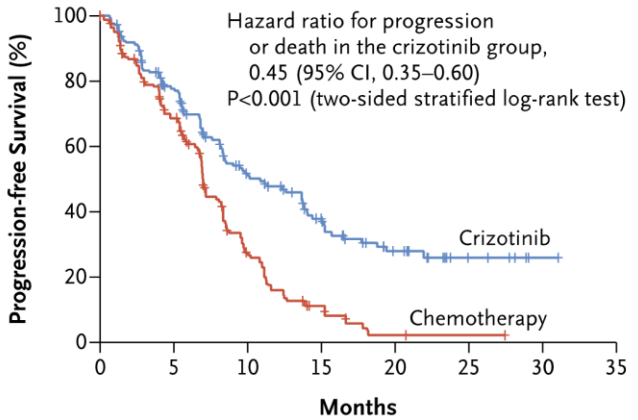
Schiller JH et al. *N Engl J Med*. 2002

How Its Going

PROFILE 2014

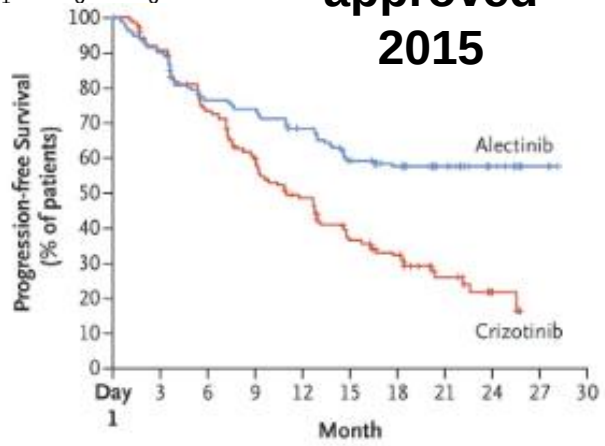
ALEX 2017

Alectinib for ALK+ approved 2015



No. at Risk								
Crizotinib	172	120	65	38	19	7	1	0
Chemotherapy	171	105	36	12	2	1	0	0

- **N=303,**
- **ORR 83%**
- mPFS 35 mos vs 11 mos
- Clear efficacy benefit

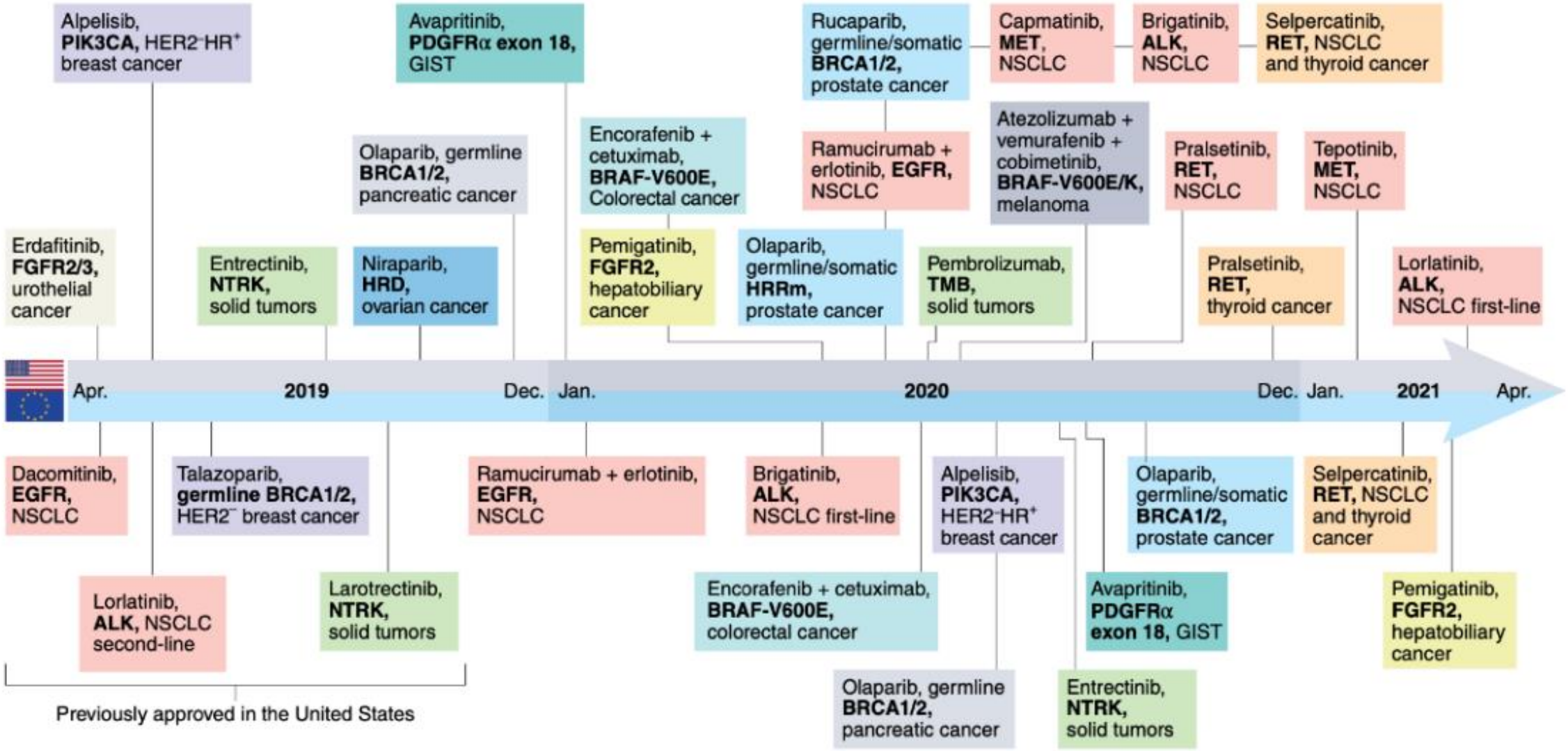


No. at Risk										
Alectinib	152	135	113	109	97	81	67	35	15	3
Crizotinib	151	132	104	84	65	46	35	16	5	

Solomon, NEJM 2014

Peters NEJM 2017

Precision Medicine Drug Approvals 2019-2021

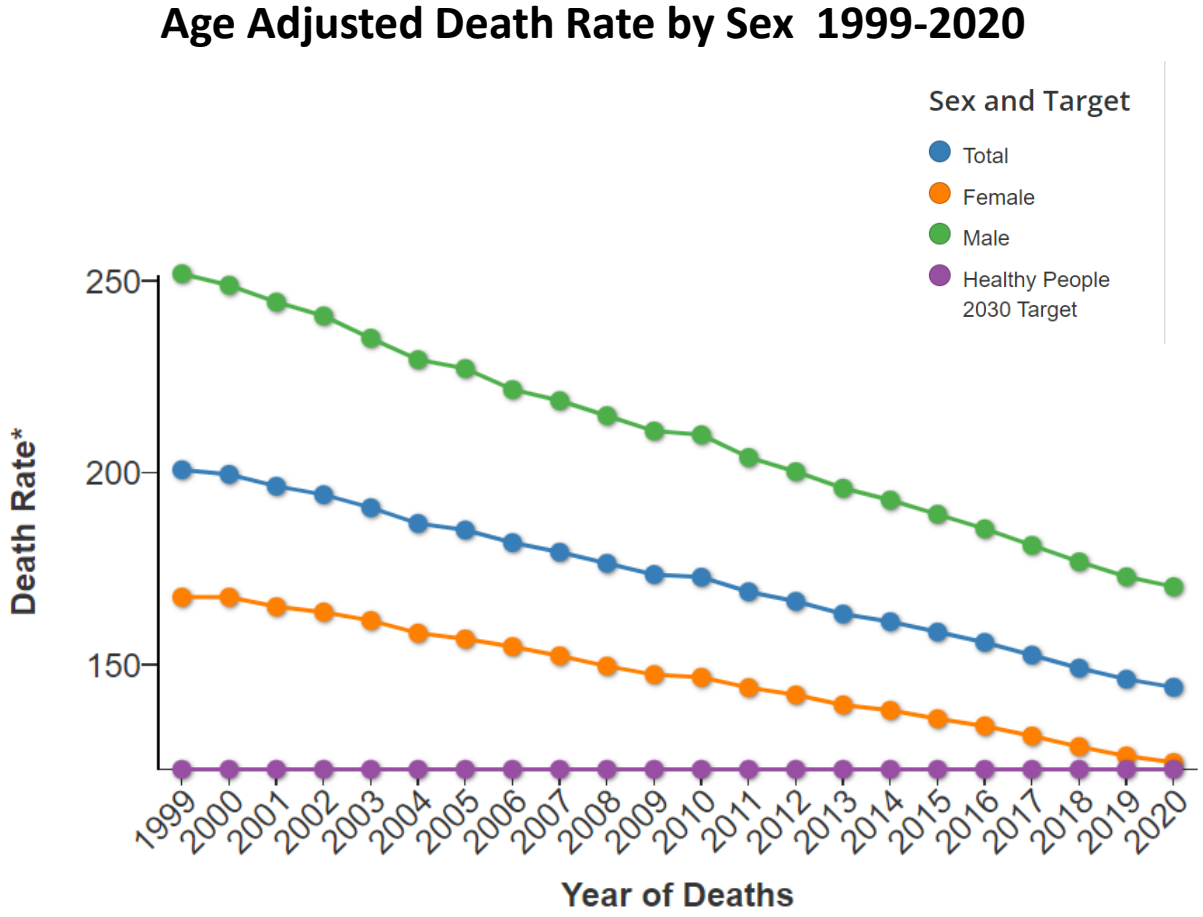


Adapted from: Mateo et al.; Nat. Medicine 2022

Decreased Cancer Mortality

- Cancer Death Rate declined by 27% from 2001 to 2020, including a 2.2% drop from 2016 to 2017, the largest single-year drop ever recorded.

- The decline in deaths from lung cancer drove the record drop. Deaths fell from about 3% per year from 2008 - 2013 to 5% from 2013 - 2017 in men and from 2% to almost 4% in women.



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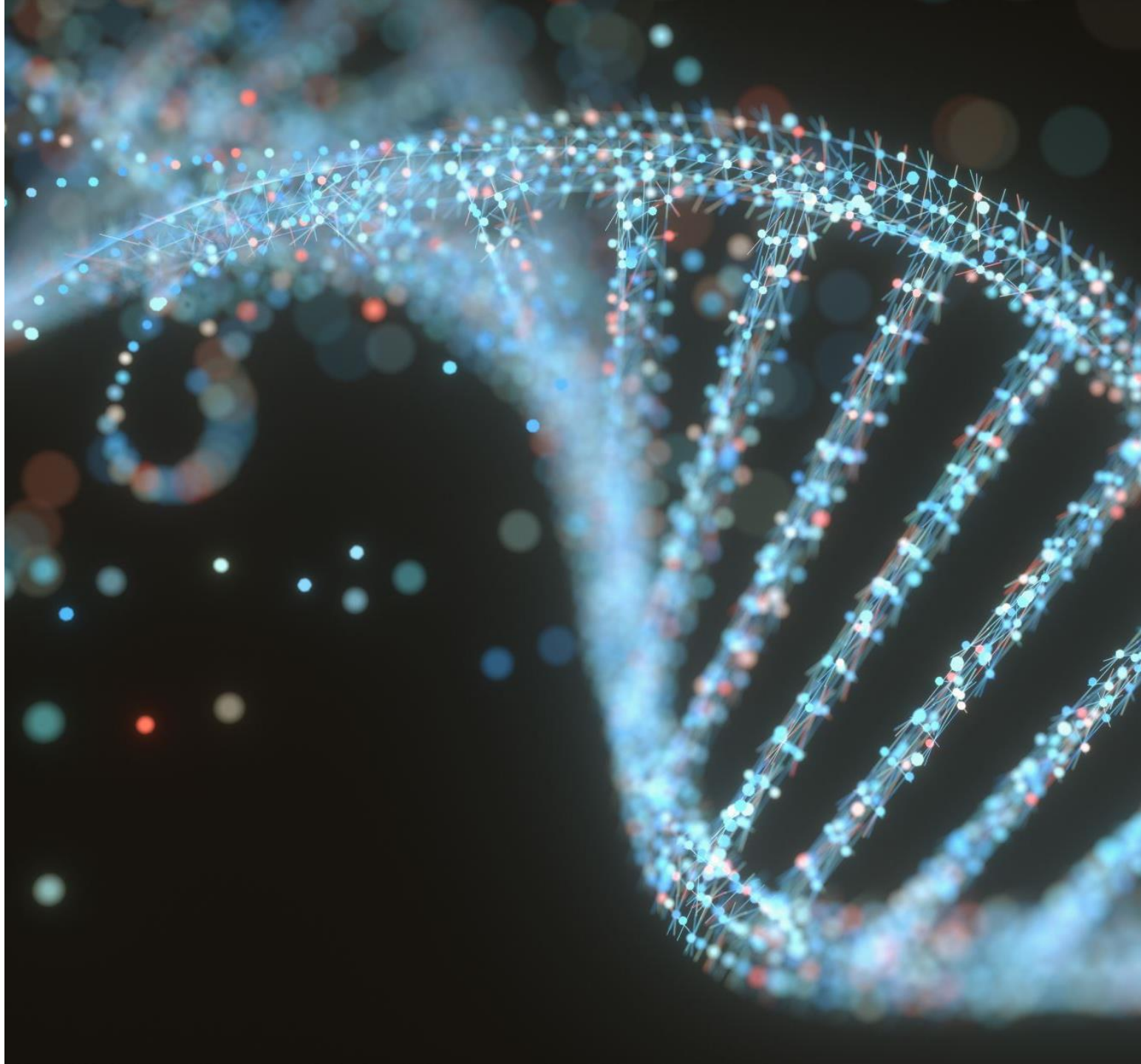
Limitations of Precision Medicine

- Despite an expanding body of evidence supporting the clinical value of genomic testing, it remains **underutilized** in clinical practice.

- Studies that have examined the clinical and economic value of genomic sequencing show that **many patients with cancer never receive indicated genomic testing.**

- Even for those who do, only **60%-75% of patients with actionable mutations receive targeted treatments** indicated by their test results and a **minority of patients are referred to biomarker-driven clinical trials**.

Q1: How to Make the Most of your Patient's Biomarker Testing?



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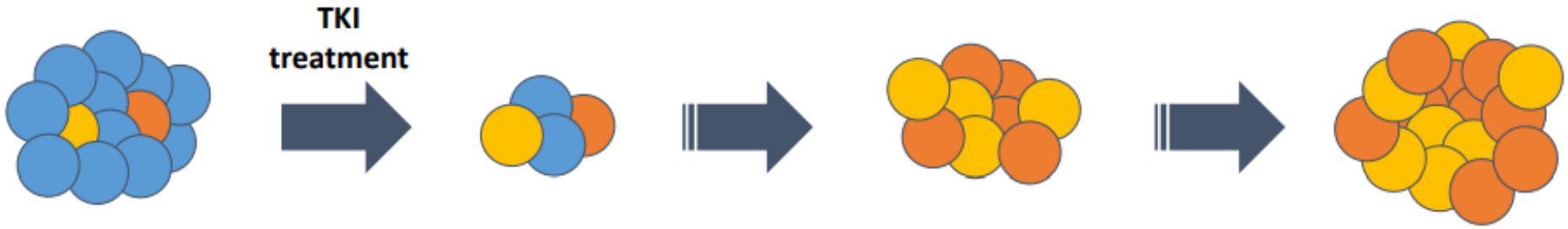
IDENTIFY MECHANISMS OF DRUG RESISTANCE & MONITOR DISEASE

Model of the emergence of TKI-resistant mutant clones[1]



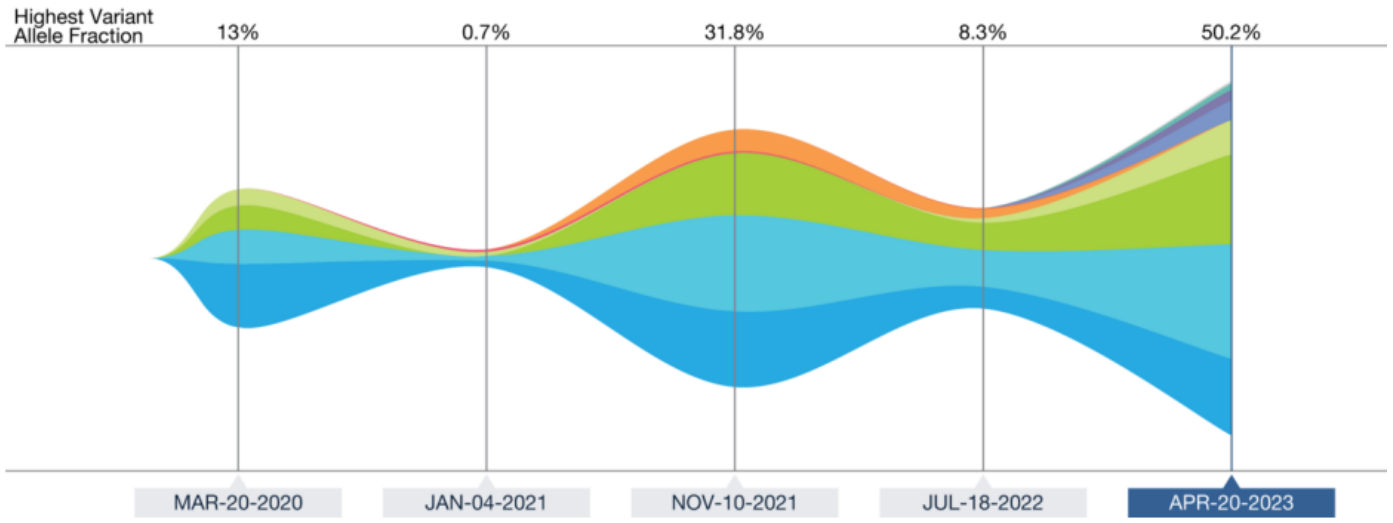
Overcoming resistance mutations in oncogenic drivers is essential for effective precision therapy

Identifying mechanisms of resistance to first generation TKI inhibitors.

Combination therapies, Therapies earlier in the disease course and developing 2nd/3rd/4th generation TKI inbitors

1. Lin JJ, Shaw AT. *Trends Cancer*. 2016;2(7):350-364. 2. Soria J-C et al. *N Engl J Med*. 2018;378(2):113-125.

51M w EGFR+ NSCLC w Osimertinib Resistance



Detected Alteration(s) / Biomarker(s)	Associated FDA-approved therapies	Clinical trial availability (see page 5)	% cfDNA or Amplification
EGFR C797S	⊗ Osimertinib	No	0.4%
EGFR E746_A750del (Exon 19 deletion)	✓ Afatinib, Dacomitinib, Erlotinib, Erlotinib+ramucirumab, Gefitinib	Yes	30.3%
TP53 H179Y	None	Yes	50.2%
AKT1 E17K	None	Yes	1.3%
CCNE1 Amplification	None	Yes	Medium (++)
AR Amplification	None	Yes	Medium (++)
RB1 E137*	None	No	37.0%

- Identify Poor Risk Co-mutations: TP53
- Potential SCLC clone: Rb1
- Emerging TKI Resistance: EGFR C797S

FIND CLINICAL TRIAL OPTIONS

60F w metastatic breast cancer with progression after hormonal therapy

Summary of Detected Somatic Alterations, Immunotherapy Biomarkers & Associated Treatment Options

KEY ✓ Approved in indication ✓ Approved in other indication ⊗ Lack of response

Detected Alteration(s) / Biomarker(s)	Associated FDA-approved therapies	Clinical trial availability (see page 4)	% cfDNA or Amplification
ESR1 D538G	⊗ Anastrozole, Exemestane, Letrozole	Yes	0.3%
ESR1 Y537N	⊗ Anastrozole, Exemestane, Letrozole	Yes	0.08%
BRCA1 R1203*	✓ Olaparib, Rucaparib, Talazoparib	Yes	8.1%

NIH U.S. National Library of Medicine

ClinicalTrials.gov

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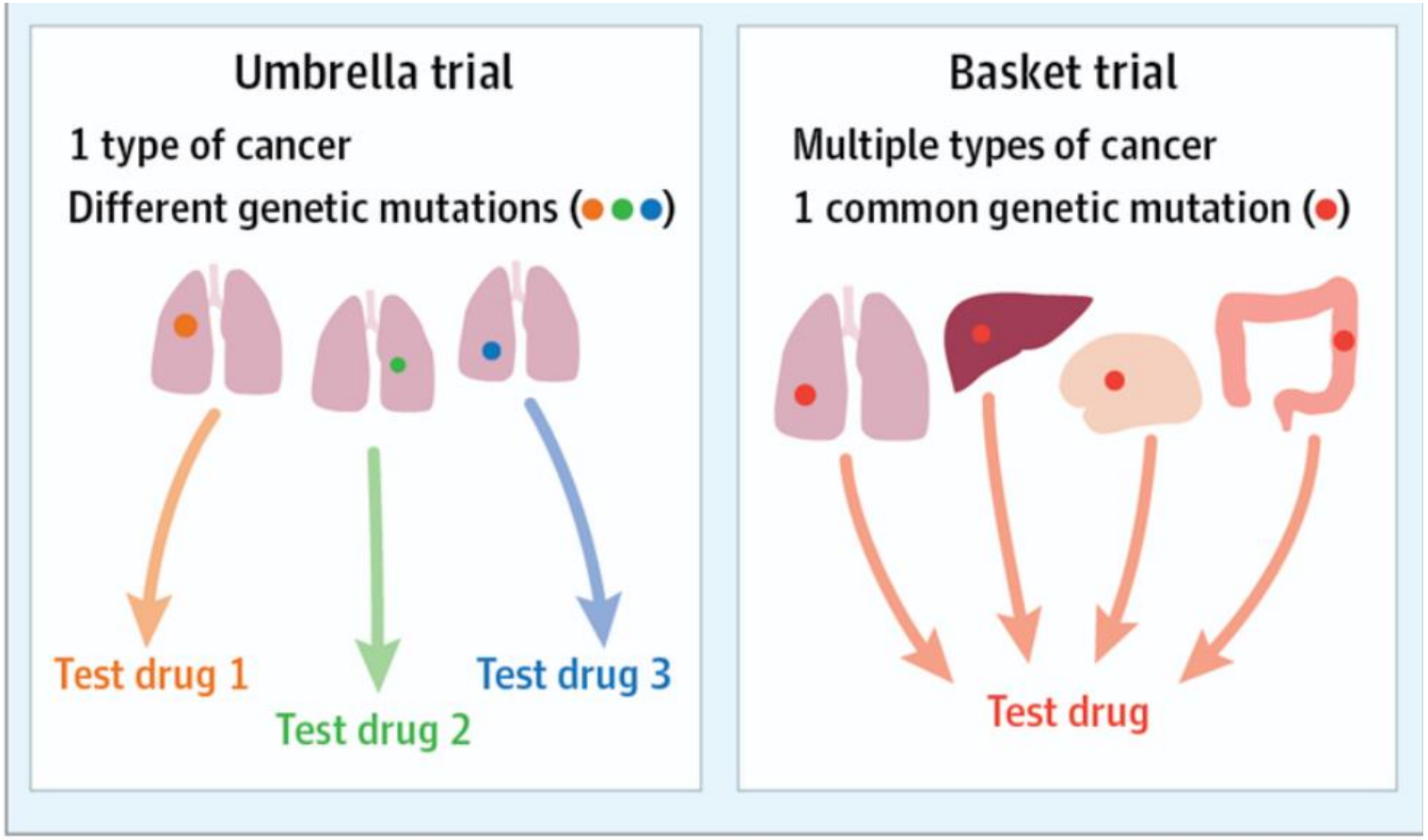
Home > Search Results > Study Record Detail ☐ Save this study

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer (TAPUR)

✓ Group 14 (BRCA1/2; ATM)

Participants receive olaparib - dosage, frequency and duration per label; acceptable genomic matches include germline or somatic BRCA1/2 inactivating mutations; ATM mutations or deletions

Precision Medicine Trial Designs



Umbrella Trial Example:
The **Lung** Cancer Master Protocol, or **Lung**-MAP,

Basket Trials have been key to accelerate approvals of targeted and tumor agnostic therapies:

BRAF

RET

ALK

NTRK

Basket Trial Examples:

TAPUR

NCI-MATCH

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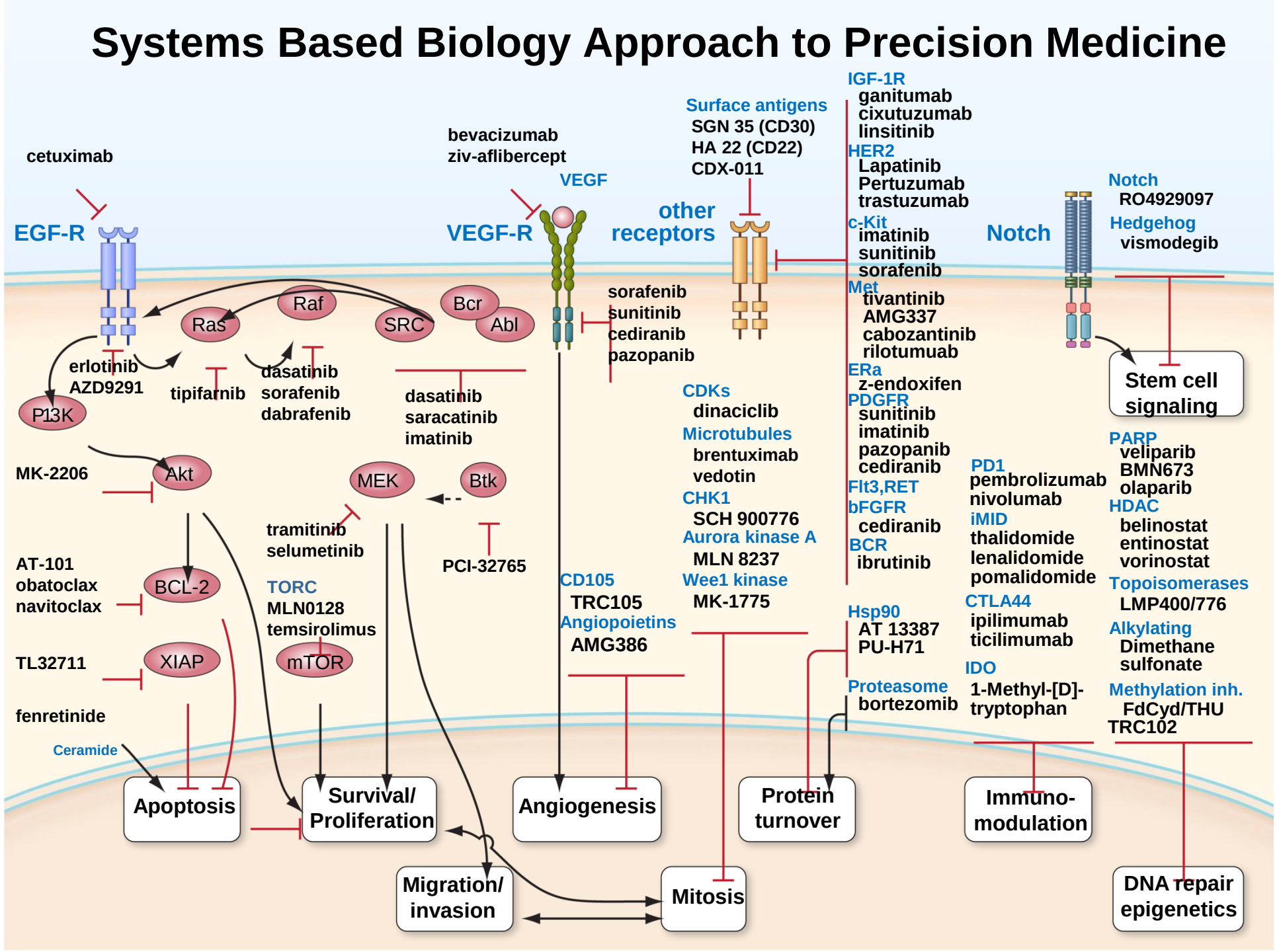
Systems Based Biology Approach to Precision Medicine

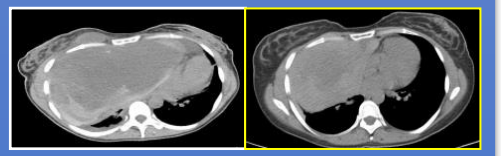


- Identify Mutation By Genetic Profiling
- Select Targeted Therapy
- Combination Therapy using selected drugs/pathways
- Proteonomic Analysis to dissect signatures of response or biomarkers

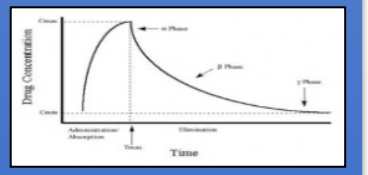
Clinical Translational Research and Cancer Biology: Bedside to Bench and Back: the N-of-One

***Clinical observations:**

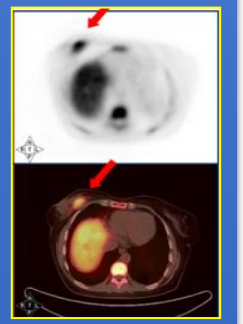
- Clinical response



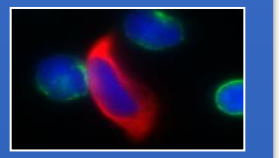
- PK



- Functional imaging



- Tumor and normal tissue PD markers
- CTCs, CECs



- Tumor-initiating cells

Patients eligible for early phase clinical trials

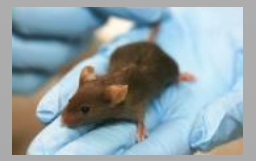
Analysis of tumor and Other tissues for pathway activation or biomarker *

Patient assigned to trial Based on molecular characterization of tumor

Patient monitoring *

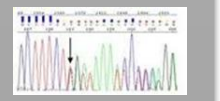
Patient monitoring: Post-treatment molecular re-analysis for response/ resistance *

Non-clinical models for targets

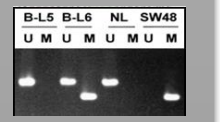


Translational research with clinical models

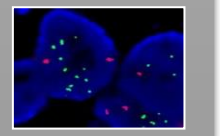
- Sequencing



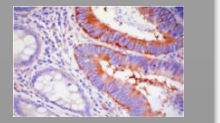
- Methylation



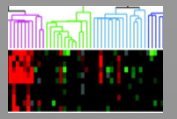
- FISH



- IHC

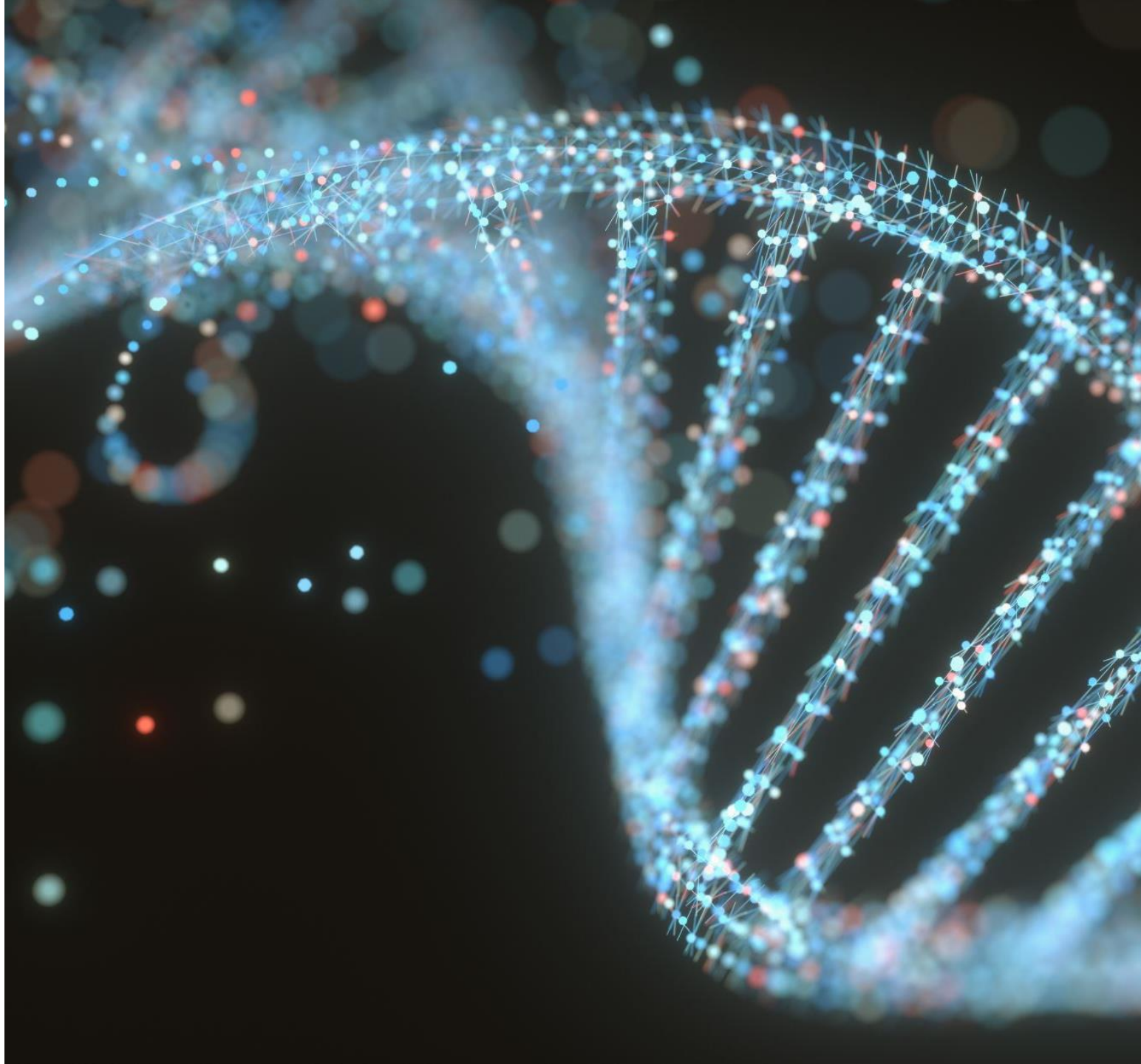


- Expression array



NCI/NCTCN

Q2: Where to Get Help with Biomarker Testing Interpretation?



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LIMITATIONS OF PRECISION MEDICINE

editorials

Ferrying Oncologists Across the Chasm of Interpreting Biomarker Testing Reports: Systematic Support Needed to Improve Care and Decrease Disparities

Howard (Jack) West, MD[1] and Christine M. Lovly, MD, PhD[2]

"The true promise of precision medicine will only be obtained when testing is both obtained and interpreted correctly."

Recommendation to:

- standardize the interpretation and output of algorithm-based interpretations from different molecular diagnostics companies.
- Leverage artificial intelligence (AI) to replicate the interpretive process of a limited cohort of available experts

- At least half of medical oncologists report a lack of confidence in interpreting genomic data
- There is an unmet need for highly skilled molecular experts
- Expert interpretation of biomarker testing results is required for translation into clinical management
- Current biomarker expertise is limited and unequal across geographies and care settings

West and Lovly, JCO Feb 2023

Molecular Tumor Boards: Caris Molecular Tumor Board (CMTB)

Powered by Caris Life Sciences®, the CMTB provides oncologists with the opportunity to interact with leading cancer experts from across the country to obtain interpretations of molecular findings and therapeutic guidance for individual patients.

- Cases are always discussed in a de-identified manner
- A Findings Form is returned via email with potential treatment paths for consideration.
- Email secure case submissions to CMTB@CarisLS.com
  - Please provide:
    - ✓ TN# (case number on CMI report)
    - ✓ Question to the Board
    - ✓ Recent Medical Note

VIRTUAL REVIEW

- Goal of providing therapeutic guidance for individual patients
- Reviews take place virtually – CMTB application
- Reviews take 7-10 full business days
- Reviewed by a panel of Board Members from many leading cancer institutions

BI-WEEKLY MTB CALLS

- Goal of providing therapeutic guidance for individual patients
- Calls are over Zoom with Caris members and panel of external Board Members
- 3-4 cases are discussed per call
- Ordering oncologist and treatment team invited to attend

BI-MONTHLY EDUCATIONAL WEBINARS

- Goal of educating the community on important role of molecular data in treating cancer patients
- Calls are bi-monthly over Zoom with anyone internal and external invited to attend
- 2 cases are discussed per call

www.CarisLifeScience.com/CMTB

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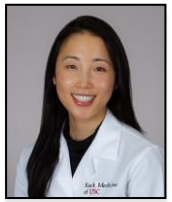

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Racial disparities in biomarker testing and clinical trial enrollment

Biomarker Testing

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**

AA = African American; NGS = next-generation sequencing

N=14,768
Stage IV NSCLC
1/2017-10/2020

Treated <120 days

Clinical Trial Participation, Logistic Regression

Among Patients who were Black/African American (AA) and White - overall NSCLC

Variable	Odds ratio (95% CI)	P-value
Biomarker testing before start of first-line therapy (yes vs no)	2.29 (1.64-3.20)	<0.0001
Ever NGS (yes vs no)	2.41 (1.56-3.70)	<0.0001
Race (Black/AA vs White)	0.45 (0.26-0.79)	0.005

Among all covariates evaluated, the additional factors associated with clinical trial participation among Black and White patients included: age at diagnosis, histology, stage III vs IV, and practice volume

Case Presentation Discussion

Specific Question(s) to the Faculty

Q1	Do you currently use biomarker testing for disease monitoring? Or identification of resistance pathway?
Q2	When was the last time that you identified a clinical trial based on genomic profiling?
Q3	Where do you get help to clarify biomarker testing results?
Q4	How can we overcome disparities in biomarker testing?

CASE PRESENTATION

The Importance of Biomarker Testing: Expect the Unexpected

Dr. Samuel Kareff, MD, MPH

Hematology/Oncology Chief Fellow

University of Miami Sylvester Comprehensive Cancer Center/Jackson Memorial Hospital

Twitter: @SamuelKareffMD

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Case Introduction

- 77-year-old woman of Ashkenazi Jewish descent with 31-pack-year history of tobacco use, having quit 24 years prior to diagnosis, and history of multifocal early-stage adenocarcinoma.

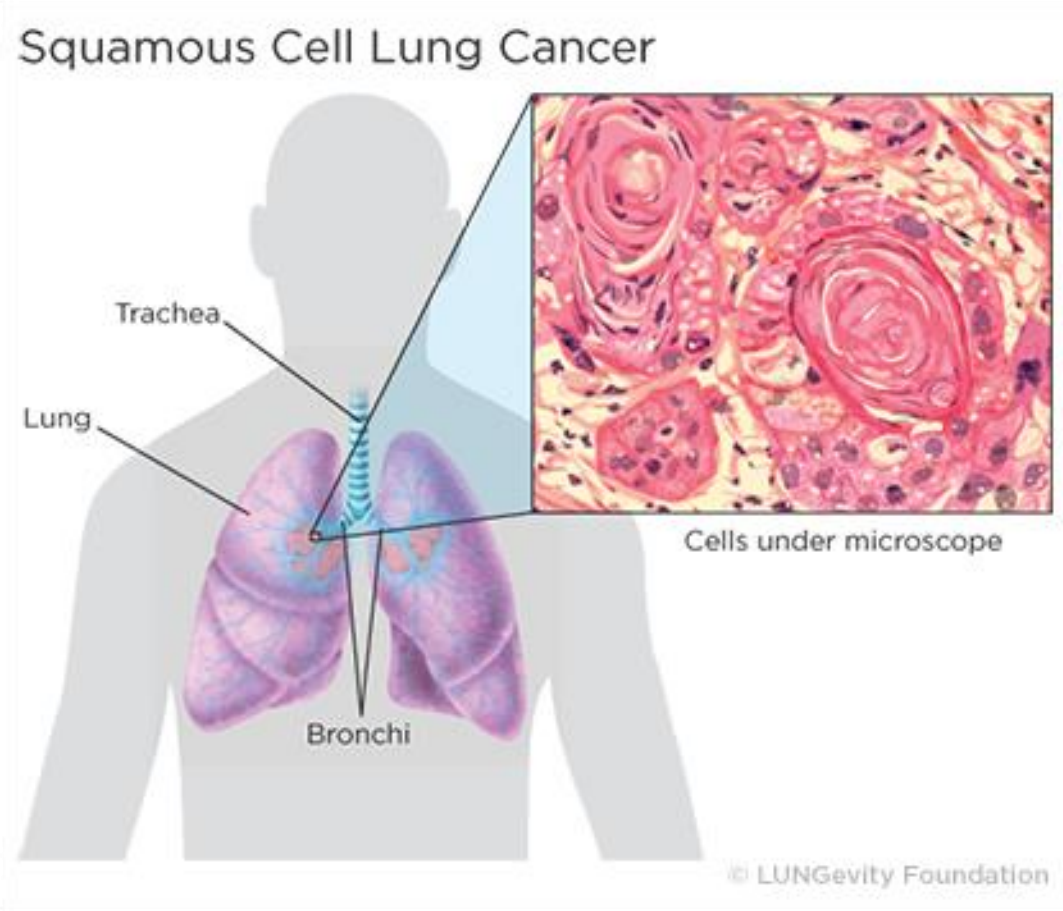
- Sept 2019: Undergoes RLL wedge and RUL lobectomy
  - NGS finds rare *EGFR* exon 18 mutation (G719A) as well as an exon 20 insertion mutation
- 2019-2021: Receives adjuvant osimertinib
- 2022: Found to have a new growing LUL lesion

Case continued

- Patient undergoes LUL wedge resection and mediastinal node dissection.

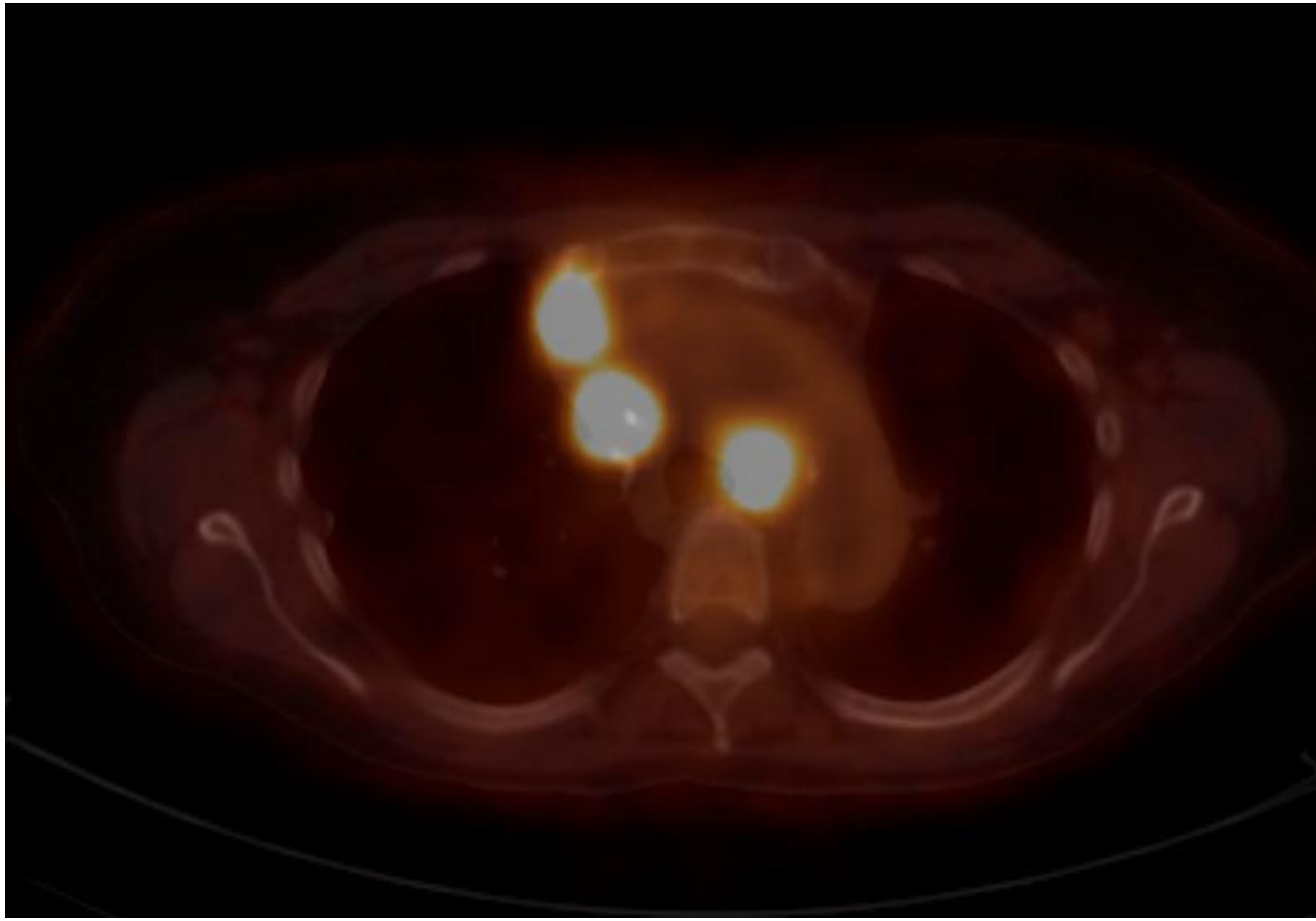
- Pathology (2022): **two** primary lesions:
  - 1) 2.6cm squamous cell carcinoma with spine cell features (pT1cN0)
  - 2) 2.0cm adenocarcinoma, lepidic predominant (70%) (pT1aN0).

- Multidisciplinary tumor board recommends surveillance.



Case continued

- Patient continues on surveillance without NGS performed.
- The patient presents to the Thoracic Surgery clinic six months later with dysphonia.
- PET/CT demonstrates a 2.7-cm adrenal mass, multiple small lytic lesions in the midthoracic spine, and cervical and mediastinal FDG-avid lymphadenopathies.
- Liquid- and solid-based NGS are sent off a new biopsy.



Next Generation Sequencing

- **Liquid:** *MET* c.3018 3028+5del (exon 14 skipping) mutation with a variant allele frequency (VAF) of 0.9%

- **Solid:** WTS and WES demonstrate *MET* exon 14 skipping mutation in RNAseq, as well as *MET* pathogenic variant exon 14 c.3075_3082+8del16 with a VAF of 46% in DNAseq
  - An additional *APC* pathogenic variant p.I1307K exon 16 c.3920T>A with VAF 61% was noted, as well as a *TP53* p.R273C exon 8 c.817C>T (VAF 19%)
  - PD-L1 2+ and 60%, microsatellite stable, tumor mutational burden-low (3), and loss of heterozygosity low (7%)

Significance of Biomarker Testing

- RNA-based testing captures greater proportion of mutations (Socinski et al. *JCOPO* 2021); IHC is not an option
- Liquid biopsy complements solid-tissue testing
- Slight benefit to treatment in the front-line setting
- Co-mutations can cause differences in efficacy

Current NCCN Guidelines

PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- **Molecular Targets for Analysis**
  - **In general, the mutations/alterations described below are seen in a non-overlapping fashion, although between 1%–3% of NSCLC may harbor concurrent alterations.**

NCCN Guidelines recognize that concurrent mutations exist in up to 3% of cases

- **Some clinicopathologic features—such as smoking status, ethnicity, and histology—are associated with the presence of an *EGFR* mutation; however, these features should not be utilized in selecting patients for testing.**

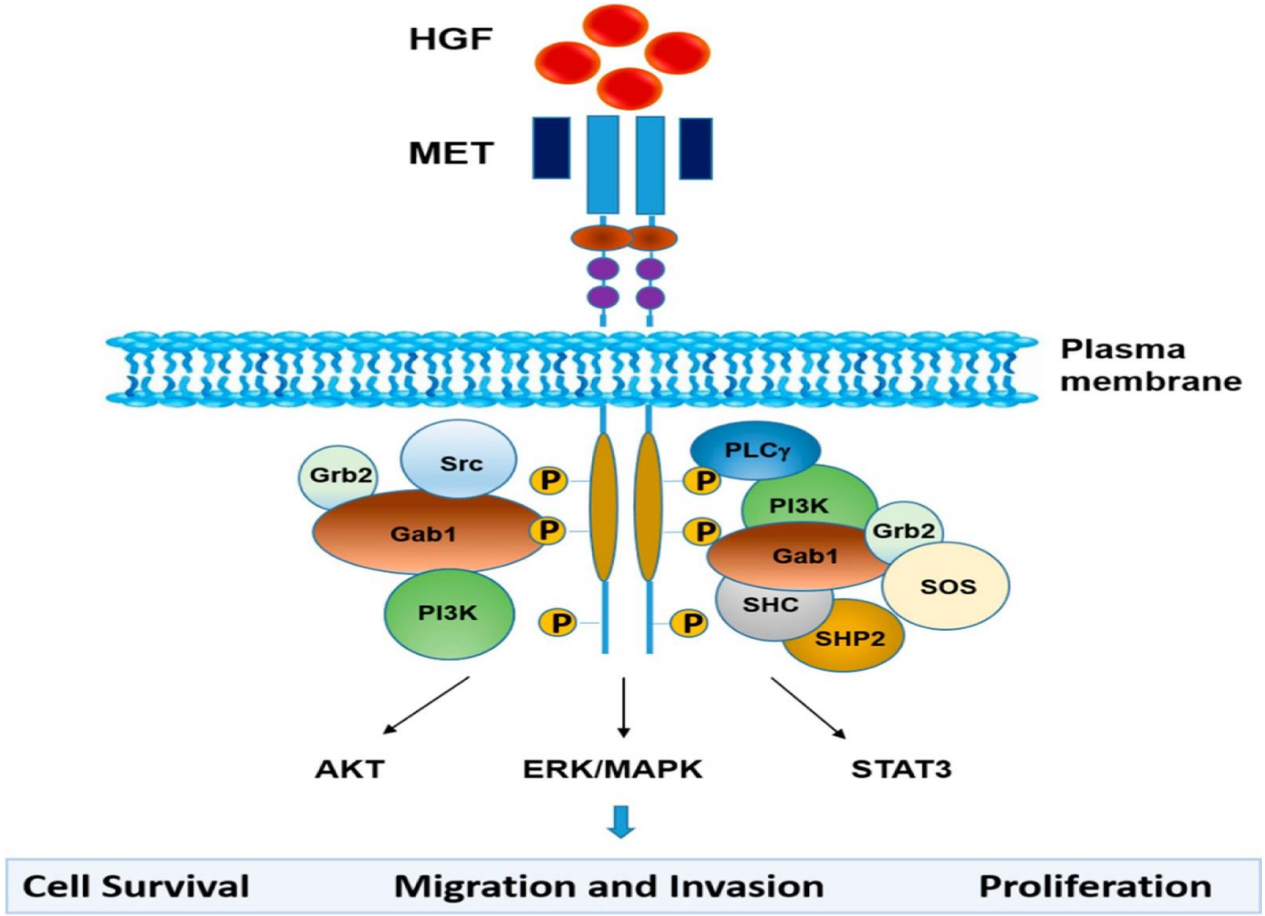
NCCN Guidelines are agnostic to histology (same for *ALK*, *ROS1*, and *ERBB2*)

- **The presence of *METex14* skipping mutation is associated with responsiveness to oral MET TKIs.**
- **A broad range of molecular alterations lead to *METex14* skipping.**
- **Testing Methodologies: NGS-based testing is the primary method for detection of *METex14* skipping events; RNA-based NGS may have improved detection. IHC is not a method for detection of *METex14* skipping.**

NCCN Guidelines incorporate both the latest and emerging data

Non-small Cell Lung Cancer. Version 3.2023, 04/13/23 © 2023 National Comprehensive Cancer Network® (NCCN®).

Significance of *MET*



Drusbosky LM, et al. Therapeutic strategies in METex14 skipping mutated non-small cell lung cancer. *J Hematol Oncol* 2021 **14**(129). https://doi.org/10.1186/s13045-021-01138-7

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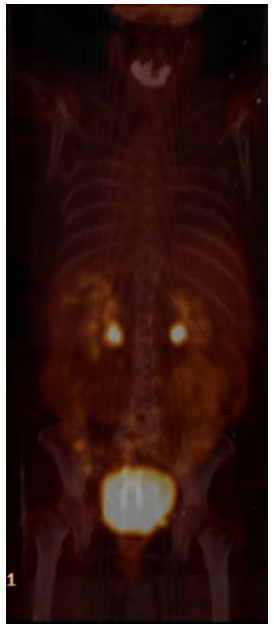
Treatment and Patterns of Resistance

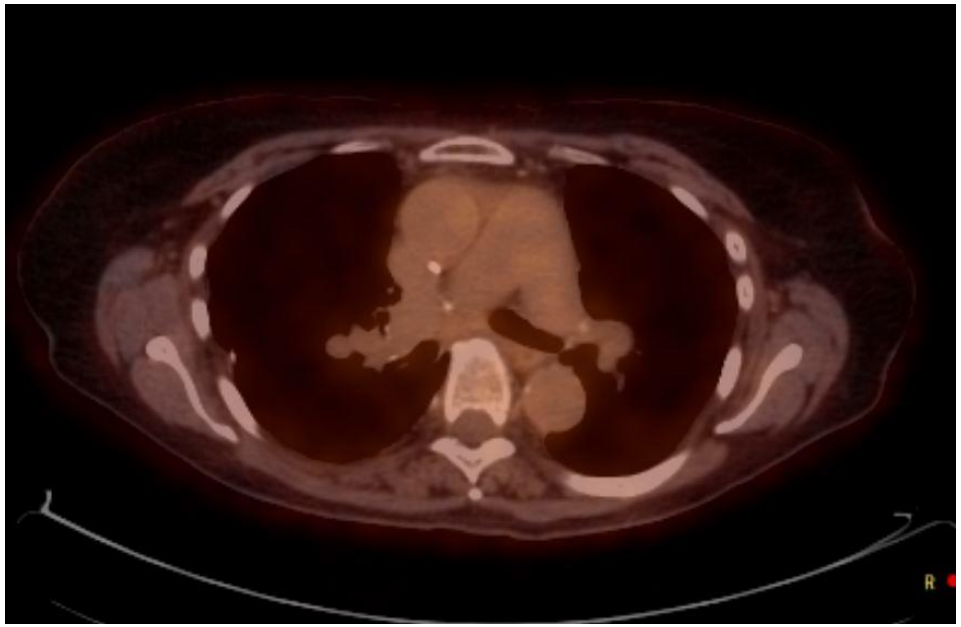
- Three types of *MET* inhibitors:
  - Type 1(a) (e.g. crizotinib)
  - Type 1(b) (e.g. capmatinib, tepotinib)
  - Type 2 (e.g. cabozantinib)
  - Type 3 (e.g. tivantinib)

- Several patterns of resistance identified
  - On-target resistance (i.e. kinase domain mutations-> change *MET*-directed TKI?)
  - Off-target resistance (i.e. activation of bypass signaling->need to look for *KRAS* amplifications or mutations, *NF1/RASA1* mutations, *PI3KCA* mutations or *EGFR* amplifications)

Patient Outcome

- Patient received one cycle of chemo + IO while NGS pending
- Later initiated on oral tepotinib 450mg daily, complicated only by Grade 1 peripheral edema
- She achieved a complete response 4 months after starting therapy





Case Presentation Discussion

Specific Question(s) to the Faculty

Q1	Would you routinely send NGS in patients with squamous cell carcinoma?
Q2	What is your practice when detecting possible pathogenic germline variants?
Q3	Do you reflex to liquid- and solid-based NGS at diagnosis when indicated?
Q4	Do you perform independent NGS testing in multifocal tumors? In early-stage cancer? At progression?

WRAP UP & NEXT STEPS

Reminder: Post-ECHO Series Assessment Survey

Help improve this ECHO Series by providing your feedback.

Please check spam folders for an email from "*redcap@vumc.org*" with a Post-ECHO Survey link.

You will also receive a Six-Month Follow-Up Survey in late November/early December.

Materials and Resources will be available soon on the ACS ECHO Website

Questions: Contact korey.hofmann@cancer.org and Leah.Mitchem@cancer.org

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Lung Cancer Biomarker Testing Funding Opportunity **Deadline Extended!**

This opportunity is open to **all** teams participating in the **NSCLC Biomarker Testing ECHO Series**

Potential Grantees must meet at least one of the following objectives:

- Address **common barriers** related to biomarker testing within the state, region, community, or system.
- Improve lung cancer biomarker **testing processes** with your health care system.
- Improve **knowledge and awareness** of testing within your **medical community.**
- Improve **knowledge and awareness** of testing within the surrounding **community**.

Join the Fight to expand Lung Cancer Biomarker Testing Access in Florida:

https://www.fightcancer.org/actions/join-our-coalition-expand-biomarker-testing-access-florida

THANK YOU!

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