Genomic-Driven Precision Oncology with Next Generation Sequencing Testing

35th Annual Park City Anatomic Pathology Update February 6-10, 2022

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Learning Objectives

1. Understand Comprehensive Genomic Profiling By NGS Testing.
2. Understand How Molecular Tumor Board Can Support Precision Oncology.
3. Review Newly FDA-Approved Oncologic Therapies In 2021.
4. A Case Study In Precision Oncology: NSCLC Patient With Brain Metastasis.

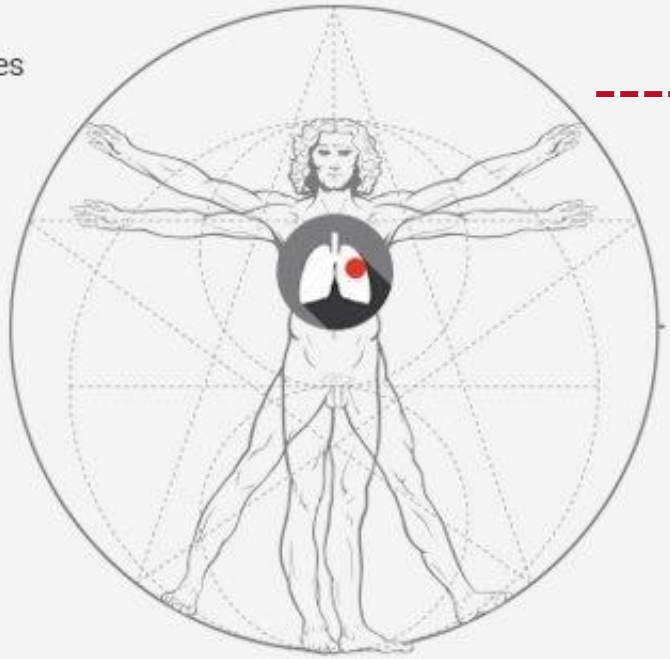
TRADITIONAL MEDICINE vs. PRECISION MEDICINE

Traditionally, radiation, chemotherapy, and surgery were the only means by which doctors could treat cancer. With precision medicine, doctors use a patient's genes to uncover clues for treating the disease.

RADIATION
- High-energy particles damage or destroy cancer cells

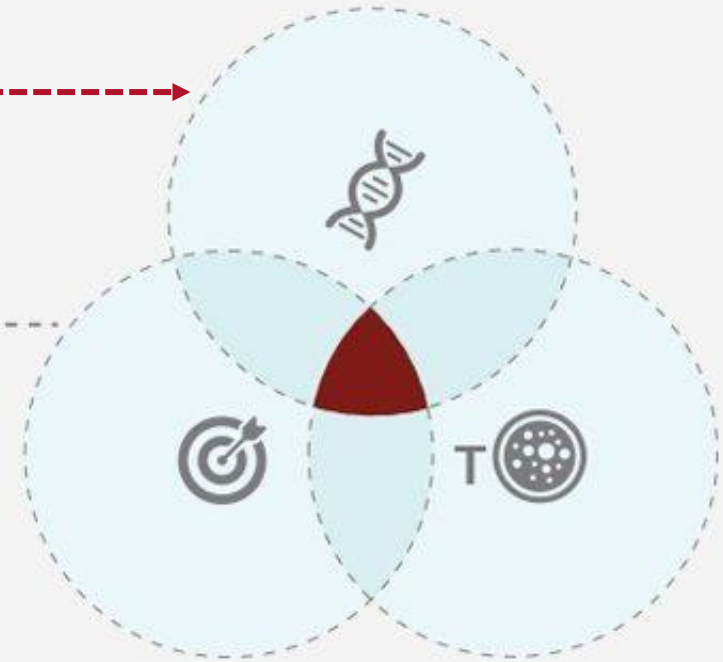
CHEMOTHERAPY
- Chemicals attack cancer

SURGERY
- Operate on part of the body to diagnose or treat cancer



NGS

Advanced Personalized Treatment



GENETICS
- Gene sequencing
- Locate cancer-causing genes

IMMUNOTHERAPY
- Identify ways to customize treatment
- Find ways to turn immune system on
- Personalize treatment with immune-activating drugs

TARGETED THERAPIES
- Drugs turn specific genes on or off

+ TRADITIONAL THERAPIES

https://healthmatters.nyp.org/precision-medicine/

Healthcare Professionals' Attitude Towards NGS Testing and Precision Cancer Medicine

- Largely positive but with some concerns.
- Lack of evidence and guidelines.
- Limited HCP knowledge about testing.
- Insurance coverage and cost to patient.
- Need for decision and implementation supports.

Journal of Oncology Practice®
Volume 15, Issue 6 297

Basics: Two Major Next Generation Sequencing Methods

Thermo Fischer

(Amplicon/Emulsion Bead PCR)

Minority Market Share

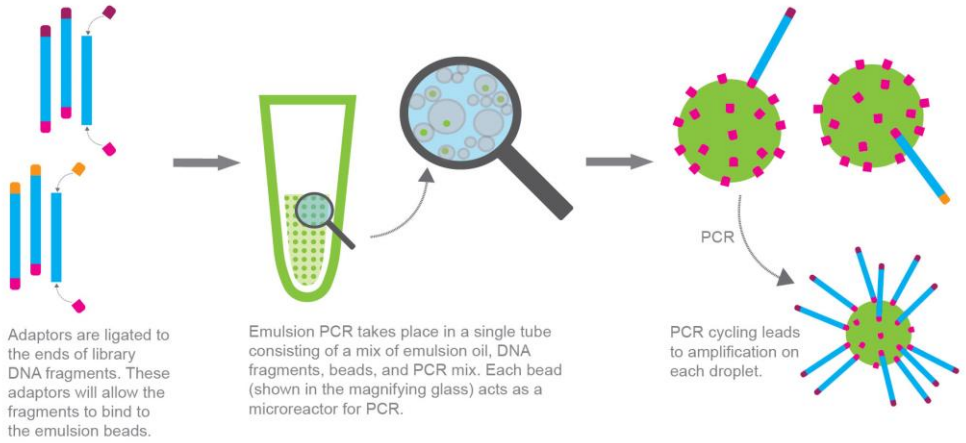


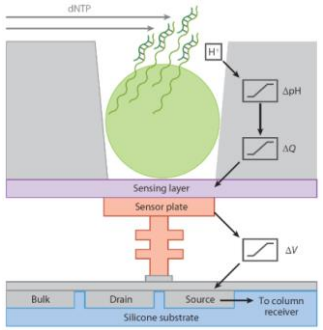
Figure 3. Conceptual illustration of emulsion PCR.

One Fragment

One Clonal Cluster

One Read

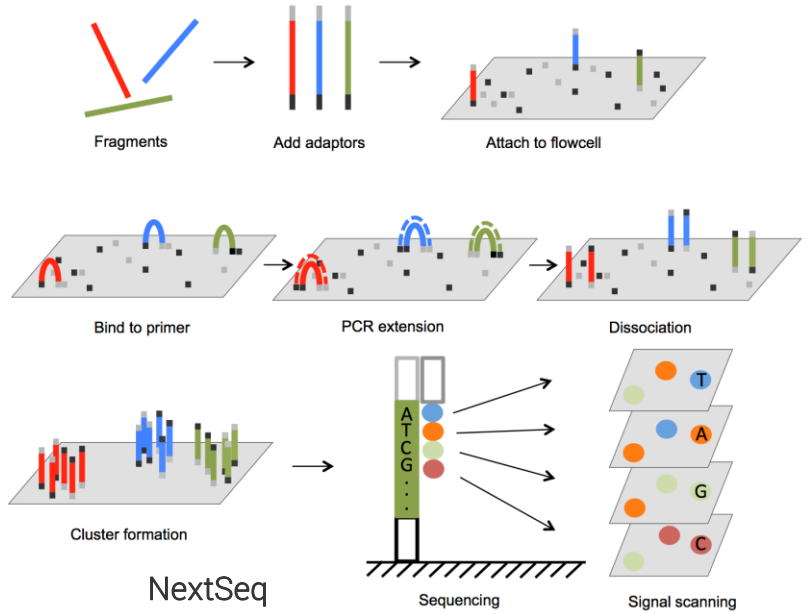
Ion Torrent PGM



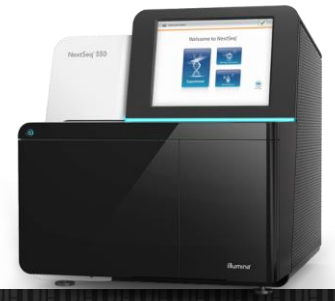
Illumina

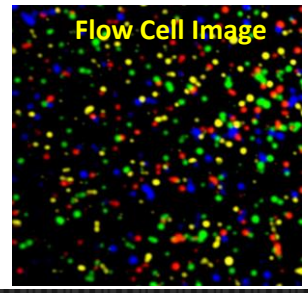
(Hybrid Capture/Flow Cell)

Majority Market Share
~ 80-90%

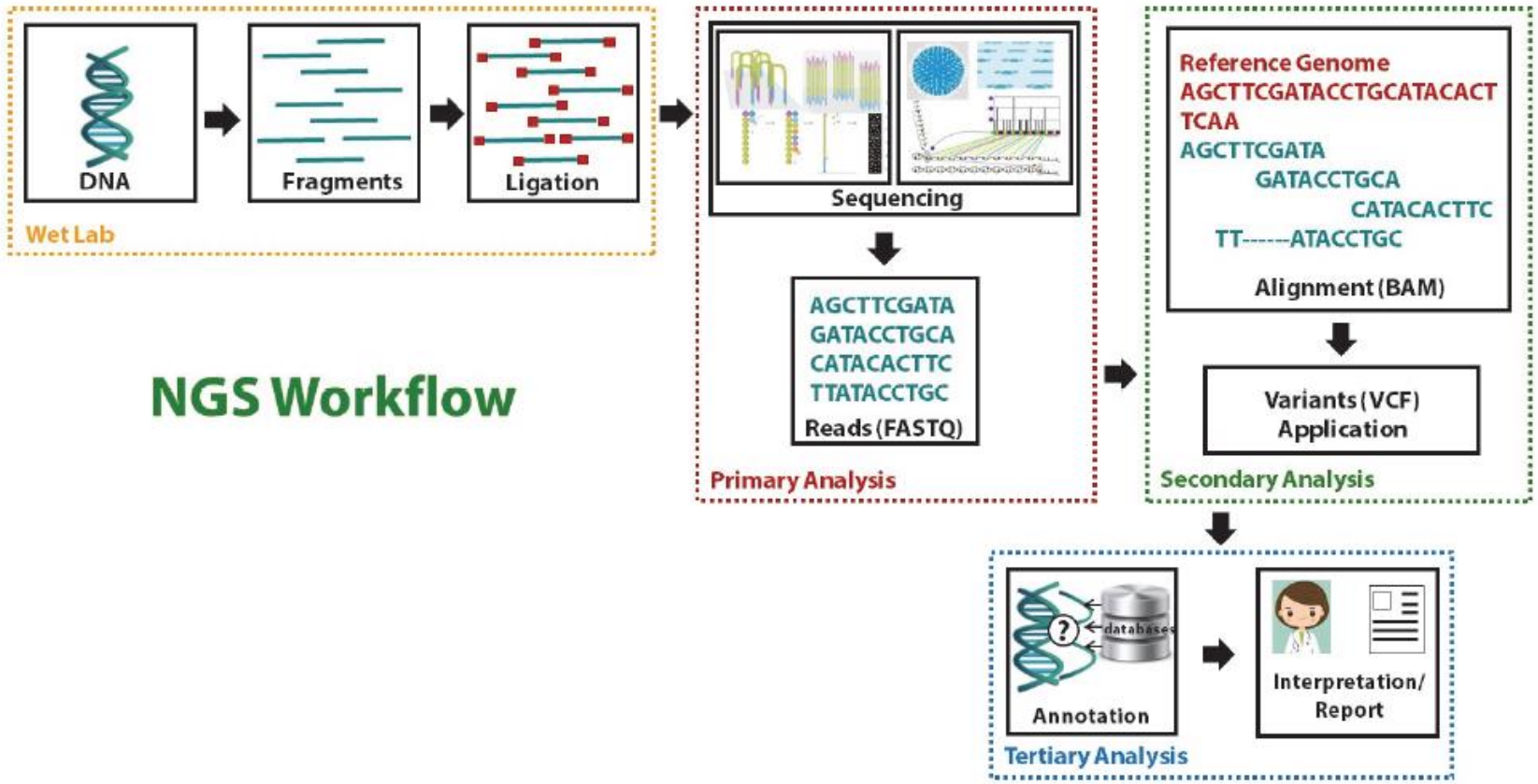


NextSeq





NGS Basics: Wet Bench to Bioinformatics

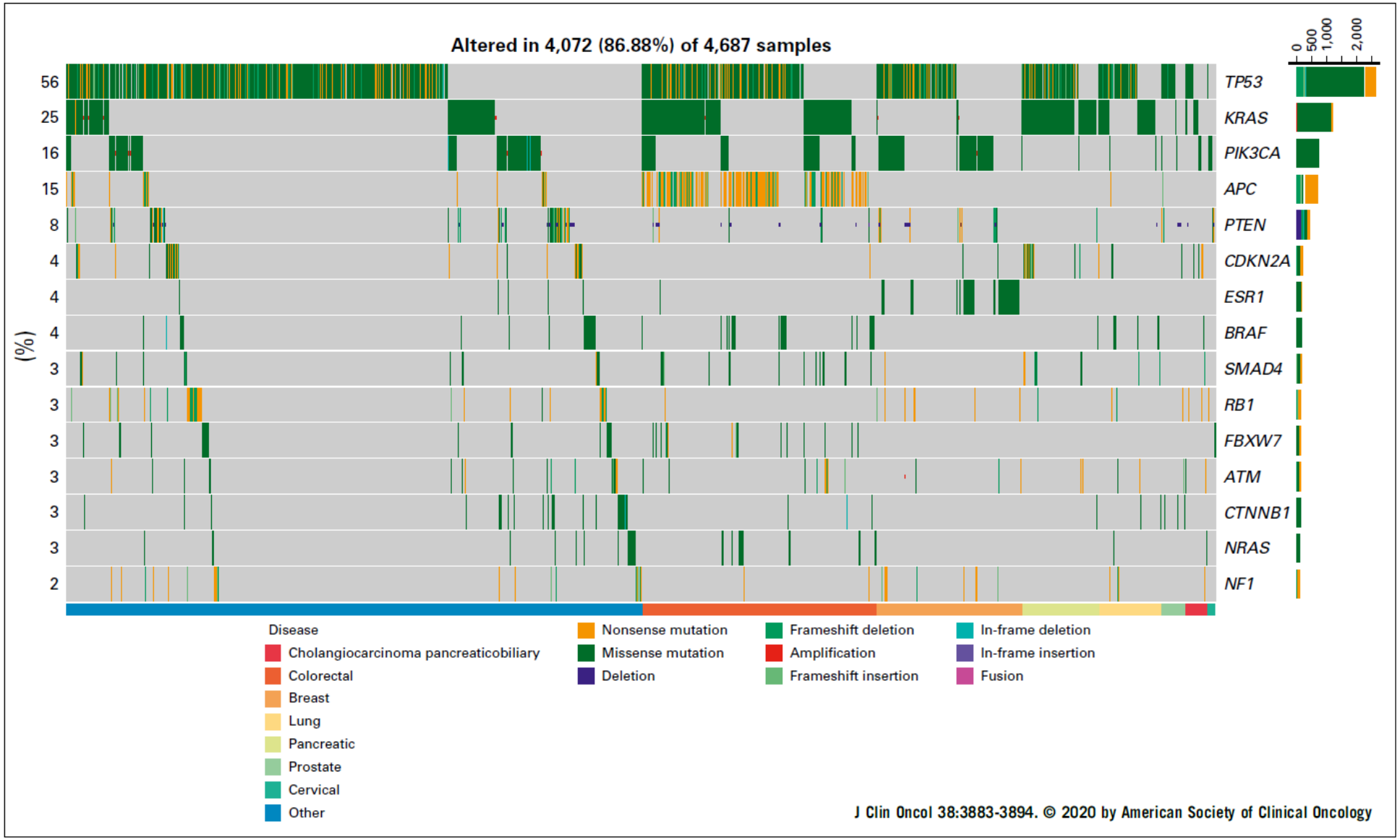


Prepared by the Association for Molecular Pathology Training and Education Committee
For More Educational Resources: *www.amp.org/AMPEducation*

NGS Basics: Potential Causes for False Negative Or False Positive Results

- Sample Issues
  - Specimen adequacy
  - Poor DNA Quality
  - Pre-Processing
- Bioinformatics Issues
  - Large deletions or insertions
  - Complex or multi-nucleotide variants
  - Difficult Regions
    - GC-bias
    - Homopolymers
    - Tandem repeats
    - Pseudogenes
- Interpretation Issues
  - UpToDate Database
  - Medical Expertise

The National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH)



- Tumor biopsy specimens from 5,954 patients with refractory malignancies.
- 38% of patients had actionable mutations.
- All available investigational therapies known with evidence of efficacy in biomarker-defined populations.
- 18% were assigned to actively enrolling treatment arms.

Understanding Comprehensive Tumor Profiling Report By NGS

Executive Summary:

This is a 59-year-old male with advanced NSCLC. Multiple genomic alterations including activating EGFR and inactivating TP53 mutations were detected. So on……

Genomic Alterations Detected:

- 4-Tier Classification
- FDA-Approved Therapy

Immunotherapy Biomarkers:

- Tumor Mutational Burden (TMB)
- Microsatellite Instability (MSI)

Variants of Undetermined Significance (VUS):

- Uncertain Clinical Significance

4-TIER Somatic Variant Classification In Cancer (AMP, ASCO, CAP)

SPECIAL ARTICLE

Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer

A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists

Marilyn M. Li,[*†] Michael Datto,[*‡] Eric J. Duncavage,[*§] Shashikant Kulkarni,[*¶] Neal I. Lindeman,[*‖] Somak Roy,[*,**] Apostolia M. Tsimberidou,[*††] Cindy L. Vnencak-Jones,[*‡‡] Daynna J. Wolff,[*§§] Anas Younes,[*¶¶] and Marina N. Nikiforova[*,**]

TIER 1 Example:
- Melanoma BRAF V600E
- Breast Cancer HER2 Amplification

TIER 2 Example:
- NSCLC with “hotspot” PIK3CA mutations
- CRC with TP53 mutations

Tier I: Variants of Strong Clinical Significance

Therapeutic, prognostic & diagnostic

Level A Evidence
FDA-approved therapy
Included in professional guidelines

Level B Evidence
Well-powered studies with consensus from experts in the field

Tier II: Variants of Potential Clinical Significance

Therapeutic, prognostic & diagnostic

Level C Evidence
FDA-approved therapies for different tumor types or investigational therapies
Multiple small published studies with some consensus

Level D Evidence
Preclinical trials or a few case reports without consensus

Tier III: Variants of Unknown Clinical Significance

Not observed at a significant allele frequency in the general or specific subpopulation databases, or pan-cancer or tumor-specific variant databases
No convincing published evidence of cancer association

Tier IV: Benign or Likely Benign Variants

Observed at significant allele frequency in the general or specific subpopulation databases
No existing published evidence of cancer association

The Journal of Molecular Diagnostics, Vol. 19, No. 1, January 2017

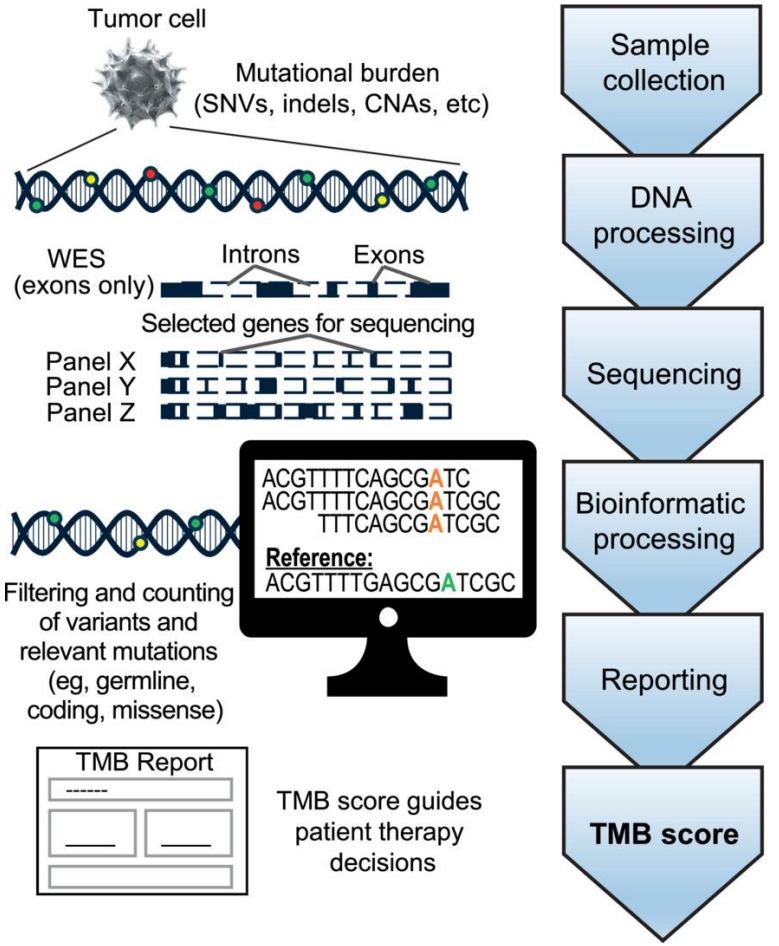
Tumor Mutational Burden (TMB)

- Measurement of the number of mutations that exists in a tumor.

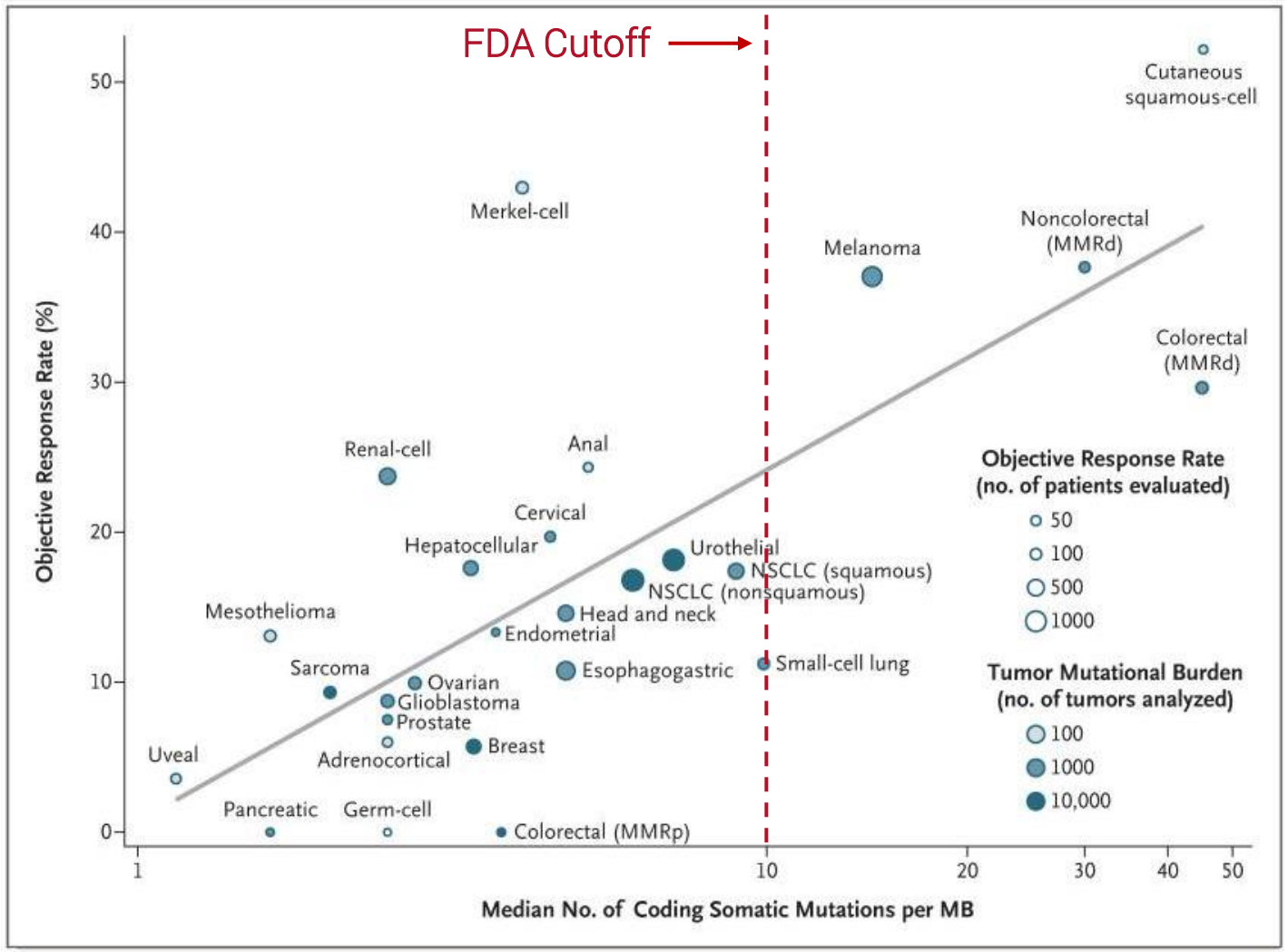
$$\text{TMB (mutations/Mb)} = \frac{\text{\# of non-synonymous somatic mutations}}{\text{Per mega-base in coding regions}}$$

- TMB is highly predictive of response to immunotherapy.
  - » FDA approval (2021) of pembrolizumab for TMB ≥ 10 in solid tumors.

- Lack of standardization regarding TMB across laboratories!



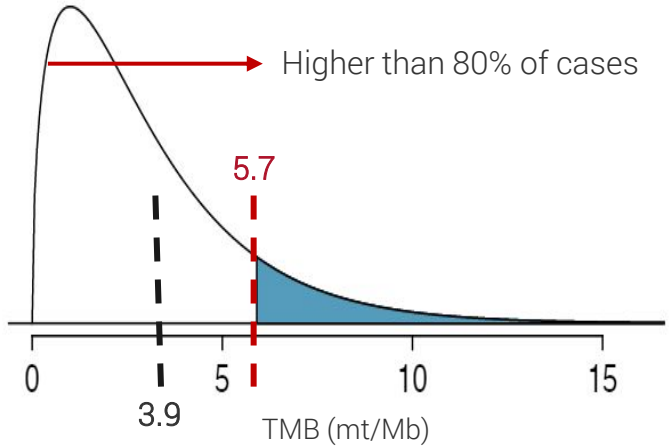
TMB and IO Efficacy Varies Across The Tumor Types



N Engl J Med. 2017 December 21; 377(25): 2500–2501

Various Ways For Reporting TMB Back To Clinicians

- Scenario #1:
  - » The estimated tumor mutational burden (TBM) for this tumor is 5.7 mutations per megabase (mt/Mb).
- Scenario #2:
  - » TMB-Low: The estimated tumor mutational burden (TBM) for this tumor is 5.7 mutations per megabase (mt/Mb).
- Scenario #3:
  - » The estimated tumor mutational burden (TBM) for this tumor is 5.7 mutations per megabase (mt/Mb) which corresponds to 80th percentile in the patient's cancer cohort.
  - » The median TMB assessed by our laboratory for patient's cancer cohort is 3.9 mt/Mb.



MSI: First FDA Approval Agnostic Of Cancer Sites

- Pembrolizumab (2017, Keytruda, Anti-PD1)
  - » 1st example of a tissue-agnostic FDA approval.
  - » Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) advanced solid tumors.
  - » Near 40% overall response rate (ORR) across 15 tumor types.
- MSI-H and dMMR Detection:
  - » Immunohistochemistry (Loss of MLH1, PMS2, MSH2, MSH6).
  - » Microsatellite instability by PCR.
  - » Microsatellite instability by NGS.

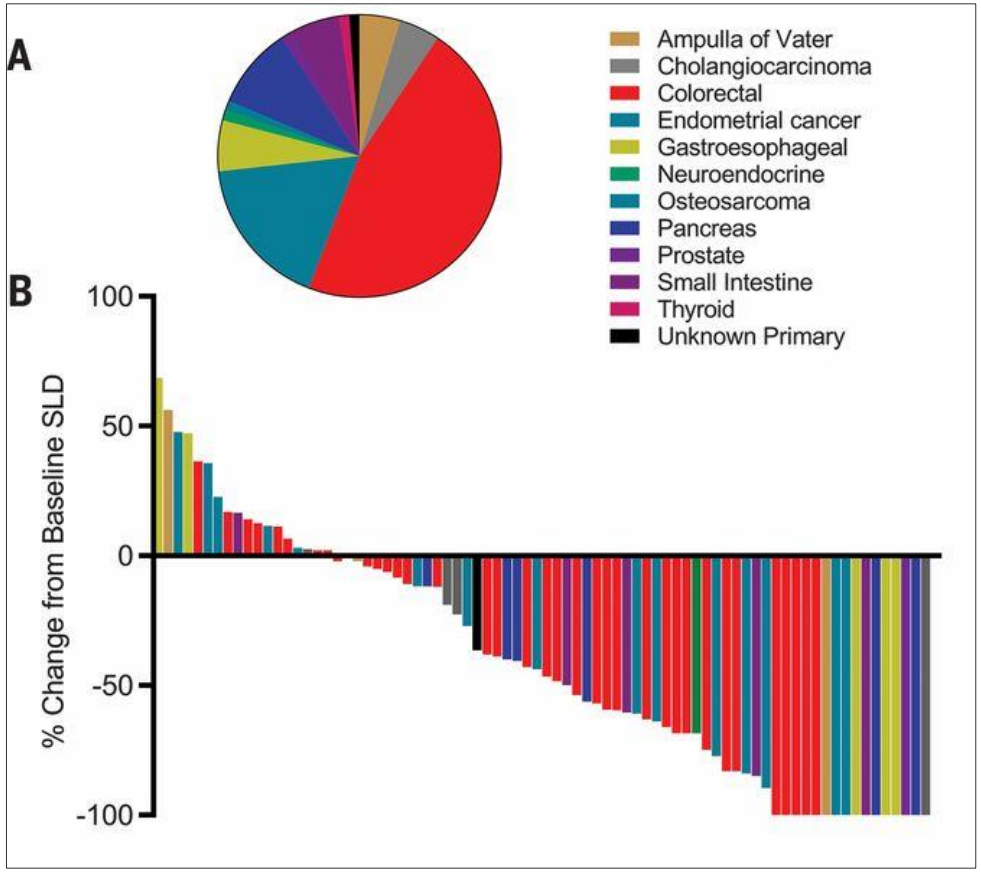
FDA NEWS RELEASE

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

Share | Tweet | Linkedin | Email | Print

For Immediate Release: May 23, 2017

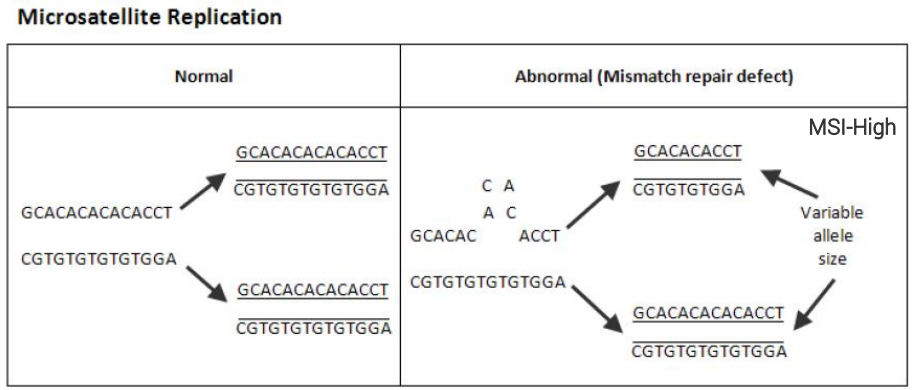
Fig. 1. Patient survival and clinical response to pembrolizumab across 12 different tumor types with mismatch repair deficiency.



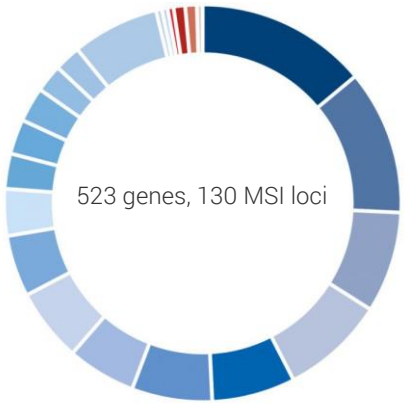
Dung T. Le et al. Science 2017;357:409-413

MSI Status Determined By Next Generation Sequencing

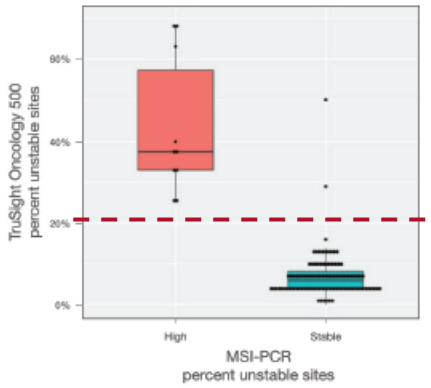
- Microsatellites are DNA motifs (1-6 BP) repeating 5-50 times.
- During replication, slippage can cause gain or loss of repeats which are then corrected by MMR proteins.
- Examine microsatellite loci (100s-1000s).
  - » Using the capture gene sequences.
  - » Dedicated specific MSI markers.
  - » Establish “baseline” statistics.
  - » Interpret fraction (%) of unstable loci to infer MSI status.

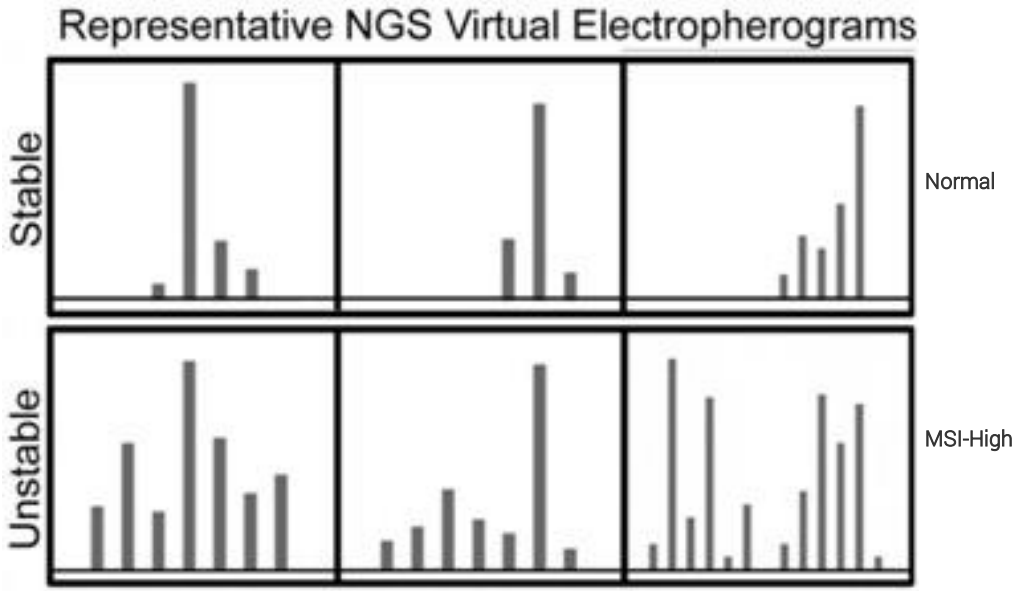


Comprehensive NGS Panel



MSI-High Cutoff





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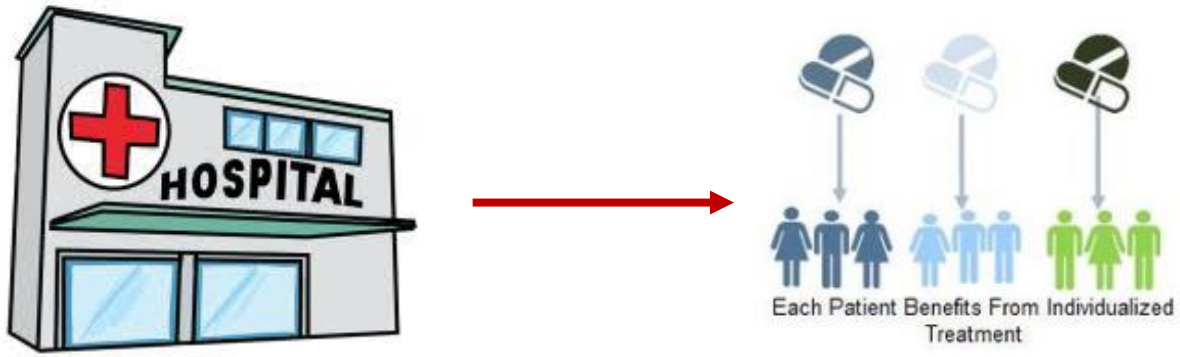
Integrating NGS Results Into Patient Care



JCO Precis Oncol 5:884-895. © 2021 by American Society of Clinical Oncology

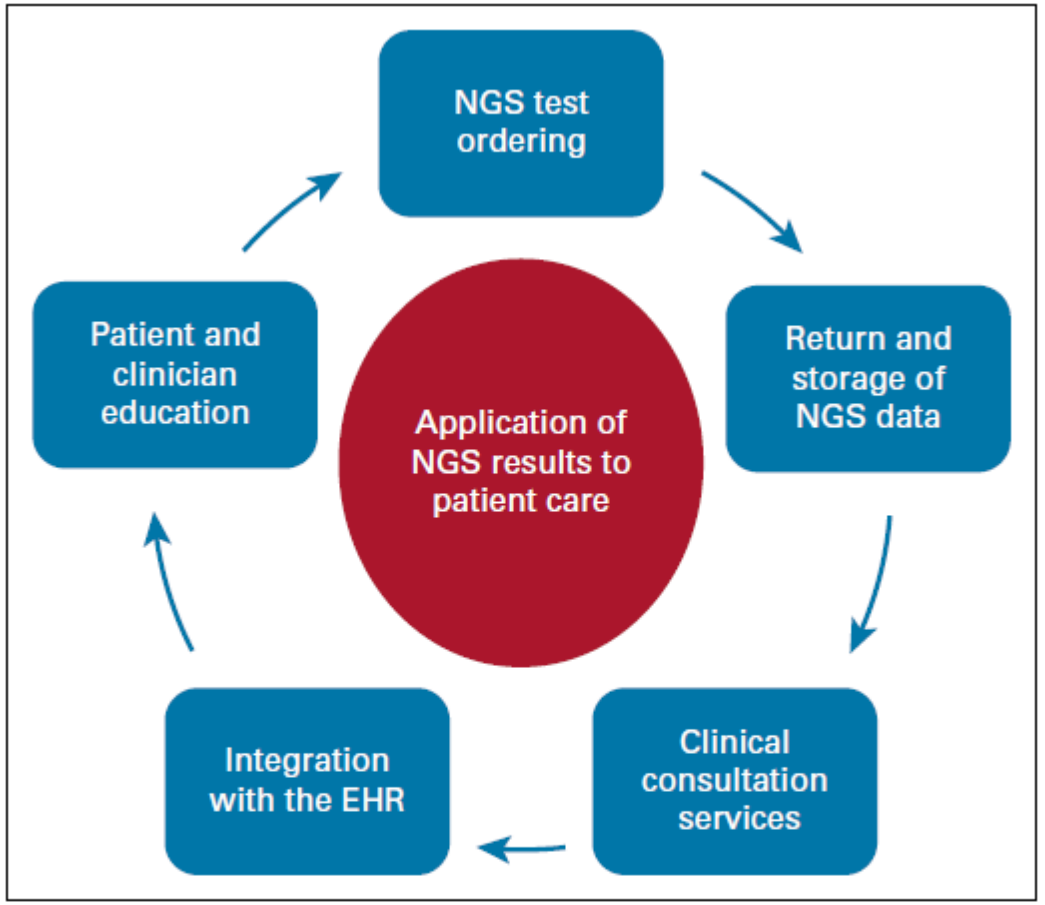
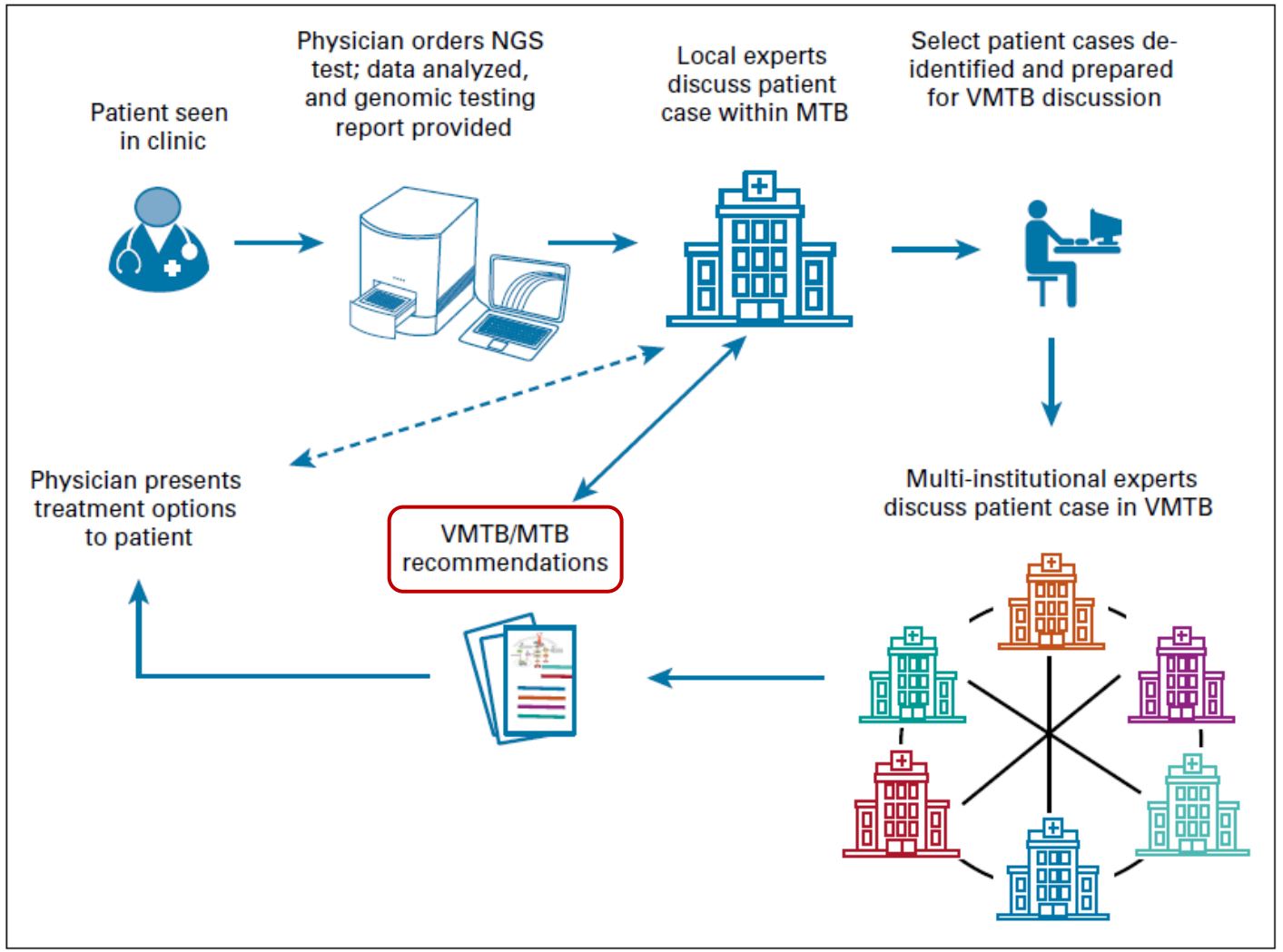


FIG 1. Key considerations for integrating somatic and germline NGS results into patient care. EHR, electronic health record; NGS, next-generation sequencing.

Incorporation of Molecular Tumor Board



Molecular Tumor Board Improves Patient Outcomes

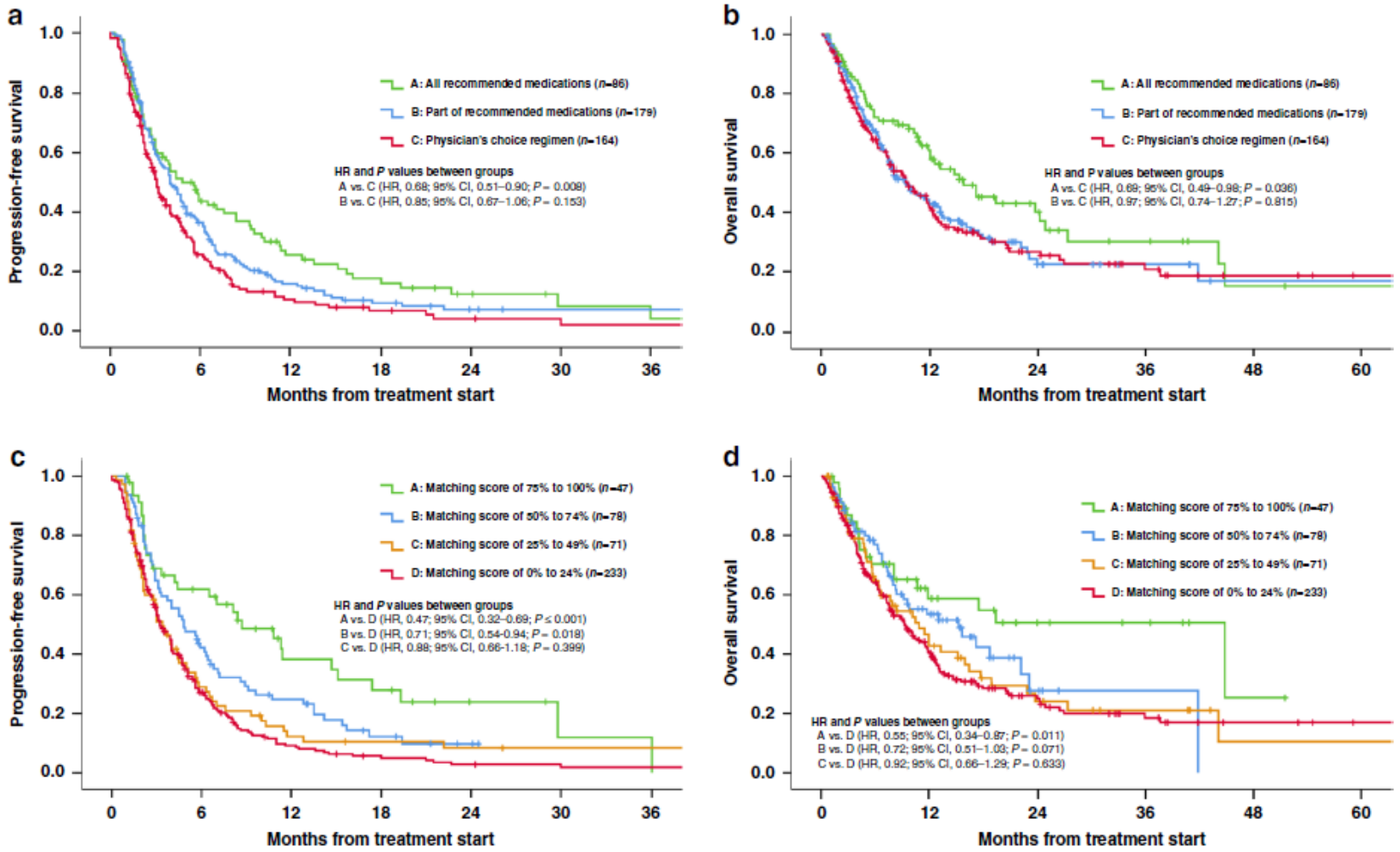


Fig. 2 Progression-free survival and overall survival according to compliance with recommendation of Molecular Tumor Board and matching scores.

NATURE COMMUNICATIONS | (2020)11:4965 | https://doi.org/10.1038/s41467-020-18613-3 |

- Outcome of 715 patients with advanced cancer presented at MTB (Academic Medical Center).
- The goal of the MTB was to develop an N-of-One treatment plan.
- MTB-recommended regimens (versus physician choice) have significantly longer progression-free (PFS) and overall survival (OS), and are better matched to therapy.
- High matching score led to overall better clinical outcomes (PFS and OS).

Molecular Tumor Board Review Improves Overall Survival In NSCLC Patients

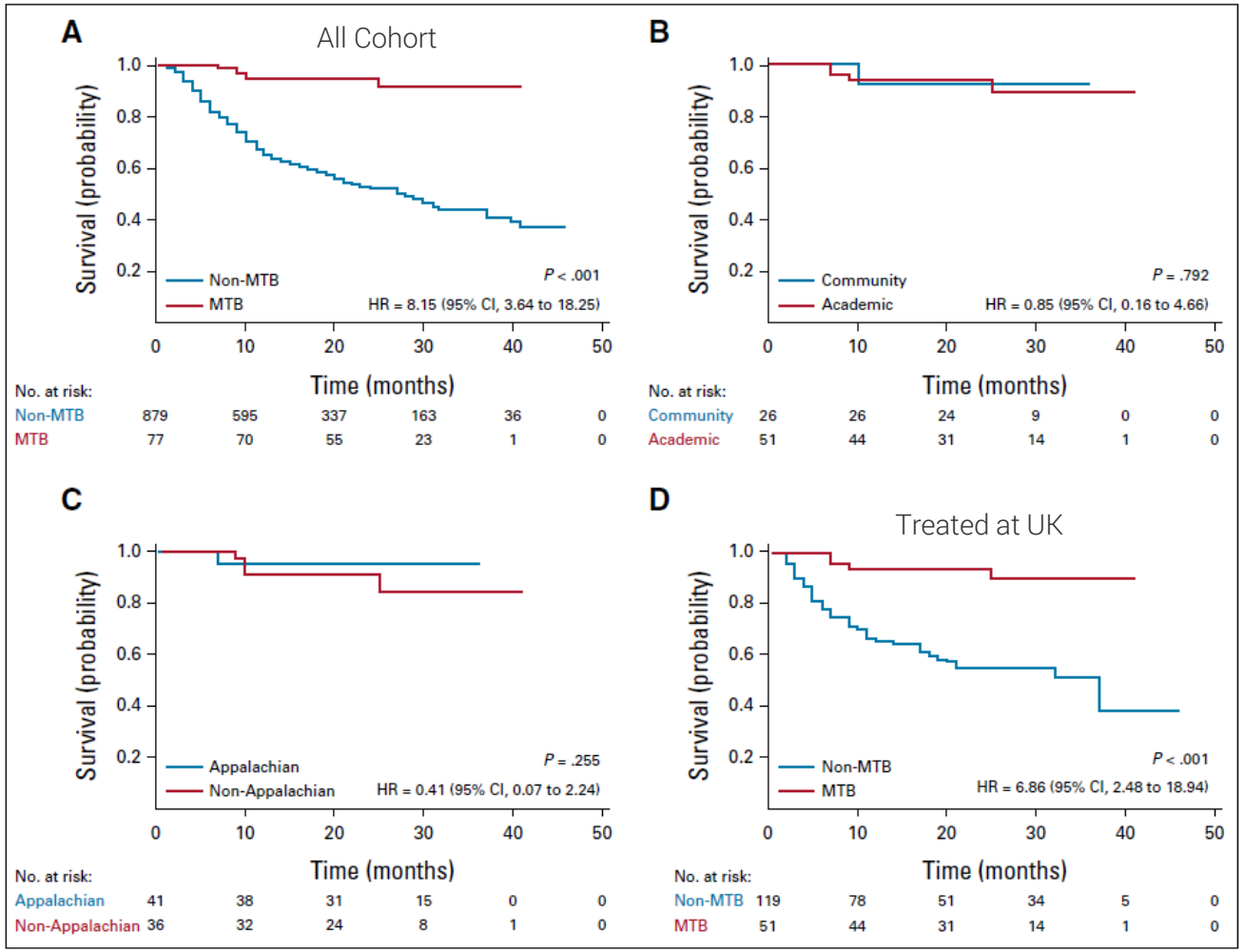


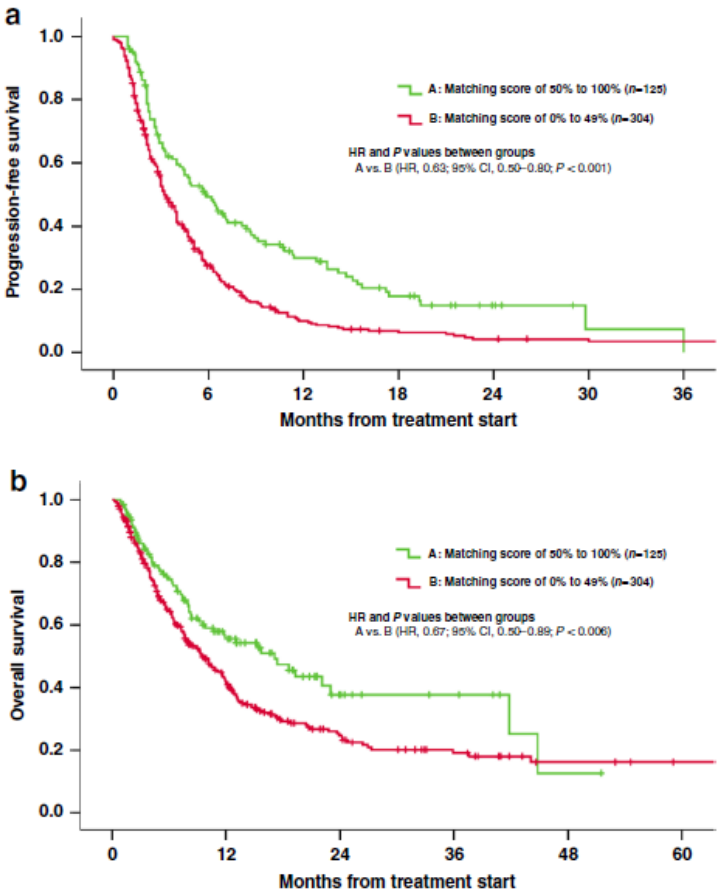
FIG 2. Kaplan-Meier plots depicting overall survival in patients on the basis of (A) all patients in cohort comparing MTB review versus no MTB review;

- A case-control study of Kentucky patients newly diagnosed with non–small-cell lung cancer between 2017 and 2019 (956 patients were included).
- Seventy-seven (8.1%) were reviewed by the MTB and classified as cases.
- The primary end point was the association between MTB review and overall patient survival.
- MTB review is an independent positive predictor of overall survival regardless of residence location.

Matching Scores and Patient Outcome

Matching score: The number of pathogenic alterations targeted by drugs given divided by total number of pathogenic alterations.

Example: Tumor has 8 pathogenic genomic alterations and the patient received two agents that targeted four alterations. Then, Matching score is 50% (4/8).



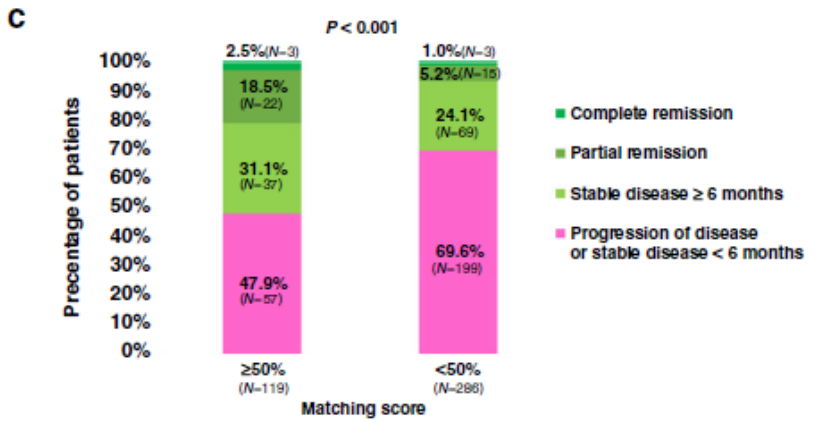
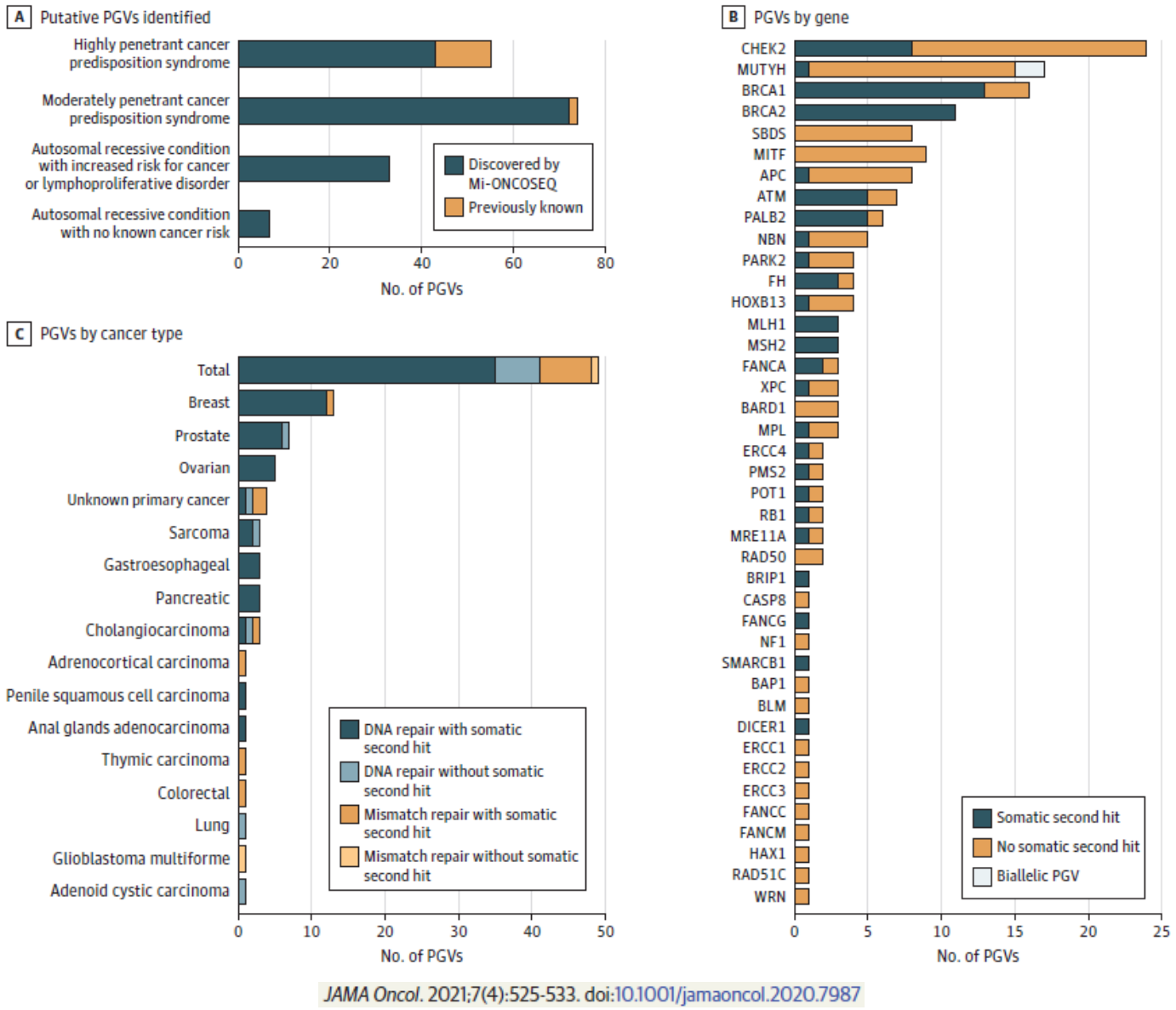


Fig. 3 Progression-free survival, overall survival and clinical benefit rate

NATURE COMMUNICATIONS | (2020)11:4965 | https://doi.org/10.1038/s41467-020-18613-3 |

Pathogenic Germline Mutations Identified By NGS

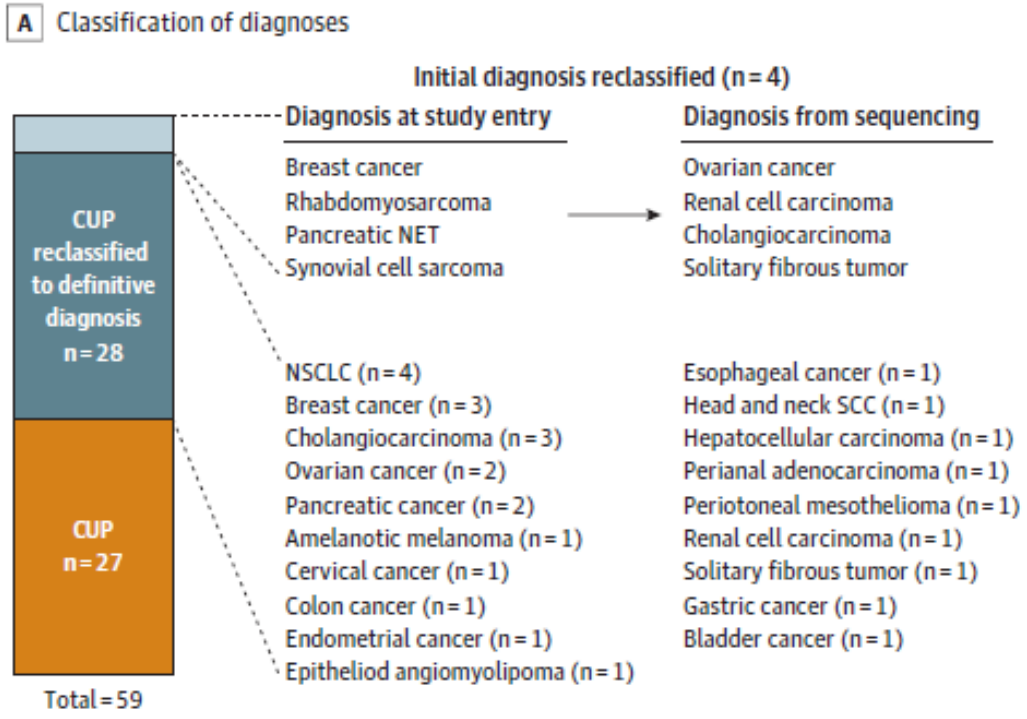


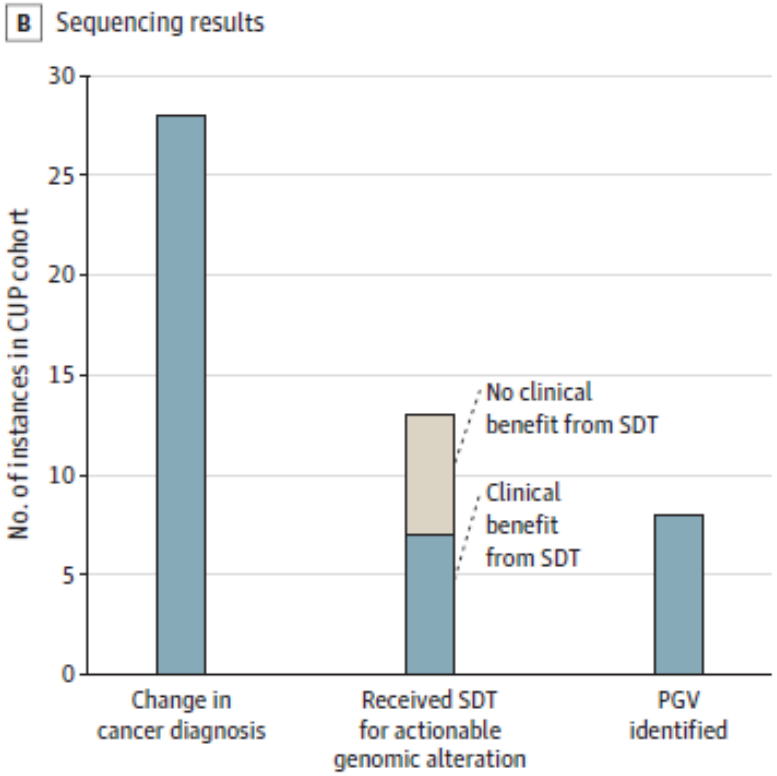
JAMA Oncol. 2021;7(4):525-533. doi:10.1001/jamaoncol.2020.7987

- 1138 patients in this cohort study underwent fresh tumor biopsy and blood sample collection for genomic profiling of paired tumor and normal DNA.
- Pathogenic germline variants (PGVs) were identified in 160 patients (15.8% of cohort), including 49 PGVs (4.8%of cohort) with therapeutic relevance.
- The high rate of therapeutically relevant PGVs identified across diverse cancer types supports a recommendation for directed germline testing in all patients with advanced cancer.
- When a pathogenic germline variant is suspected during tumor-only testing, the variant is recommended to be confirmed with a paired-normal sample according to the AMP-ASCO-CAP guidelines.

Utility of NGS Testing For Patients With Cancer Of Unknown Primary (CUP)

Figure 5. Cancers of Unknown Primary Origin in MET1000 Cohort





JAMA Oncol. 2021;7(4):525-533. doi:10.1001/jamaoncol.2020.7987

- Among 55 cases of cancer of unknown primary (CUP) origin sequenced, 28 (50.9%) were reclassified to a definitive diagnosis through RNA sequencing.
- An additional 4 cases with presumed known diagnoses at study entry were also reclassified.
- 13 patients (23.6%) received sequencing-directed therapy (SDT).
- Identification of a pathogenic germline variant (PGV) conferring increased cancer risk in 8 patients (14.5%).

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“New Era: Tissue-Agnostic” FDA-Approved Drugs

- **Pembrolizumab** (2017, Keytruda, Anti-PD-1)
  - 1st example of a tissue-agnostic FDA approval.
  - **MSI-H and dMMR** advanced solid tumors.
- **Larotrectinib** (2018, Loxo Oncology, NTRK Fusion Inhibitor)
  - Adult and pediatric solid tumors w/ **NTRK gene fusions**.
  - ORR was 75%, including 22% complete responses and 53% partial responses.
- **Entrectinib** (2019, Genentech, NTRK Fusion Inhibitor)
  - Adult and pediatric solid tumors w/ **NTRK gene fusions**.
  - ORR of 57.4% and a median duration of response of 10.4 months.
- **Pembrolizumab** (2020, Keytruda, Anti-PD-1)
  - FDA approval of pembrolizumab for **TMB ≥ 10 (mt/Mb)** in advanced solid tumors.
- **Dostarlimab-gxly** (2021, Jemperli, Anti-PD-1)
  - 2021 (April): For adult patients with **mismatch repair deficient (dMMR)** recurrent or advanced endometrial cancer.
  - 2021 (Aug): For adult patients with **mismatch repair deficient (dMMR)** recurrent or advanced solid tumors.

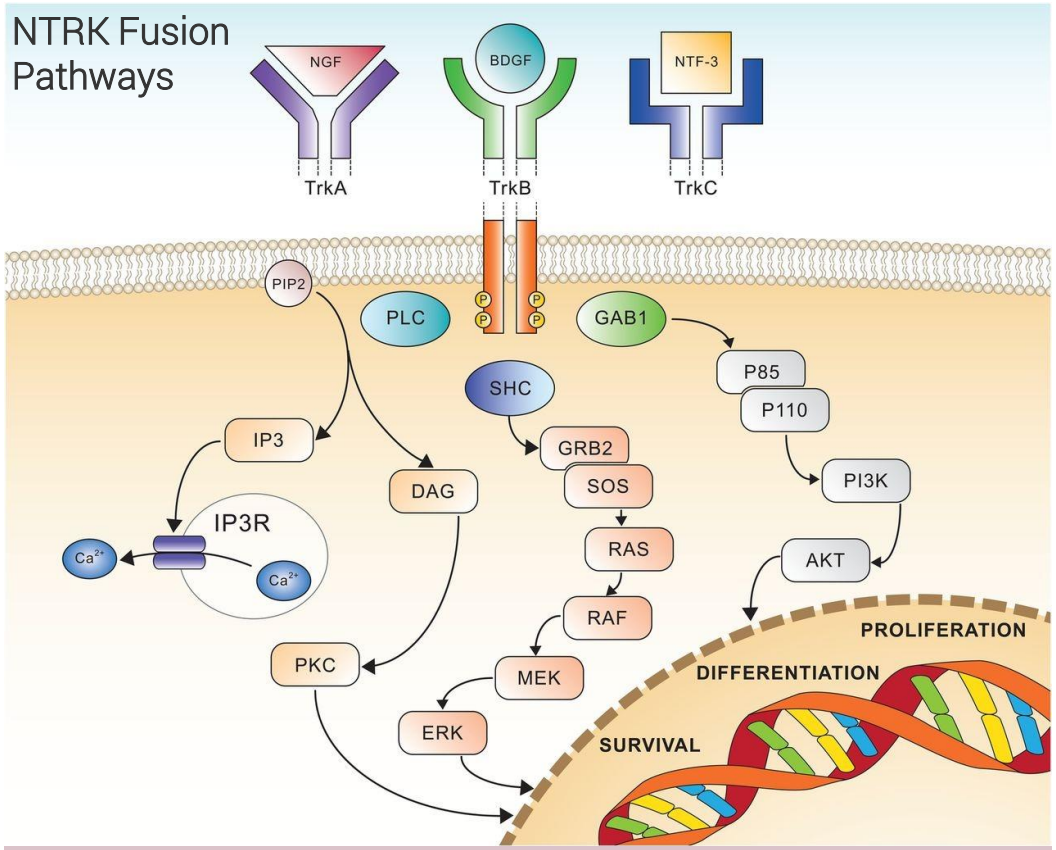
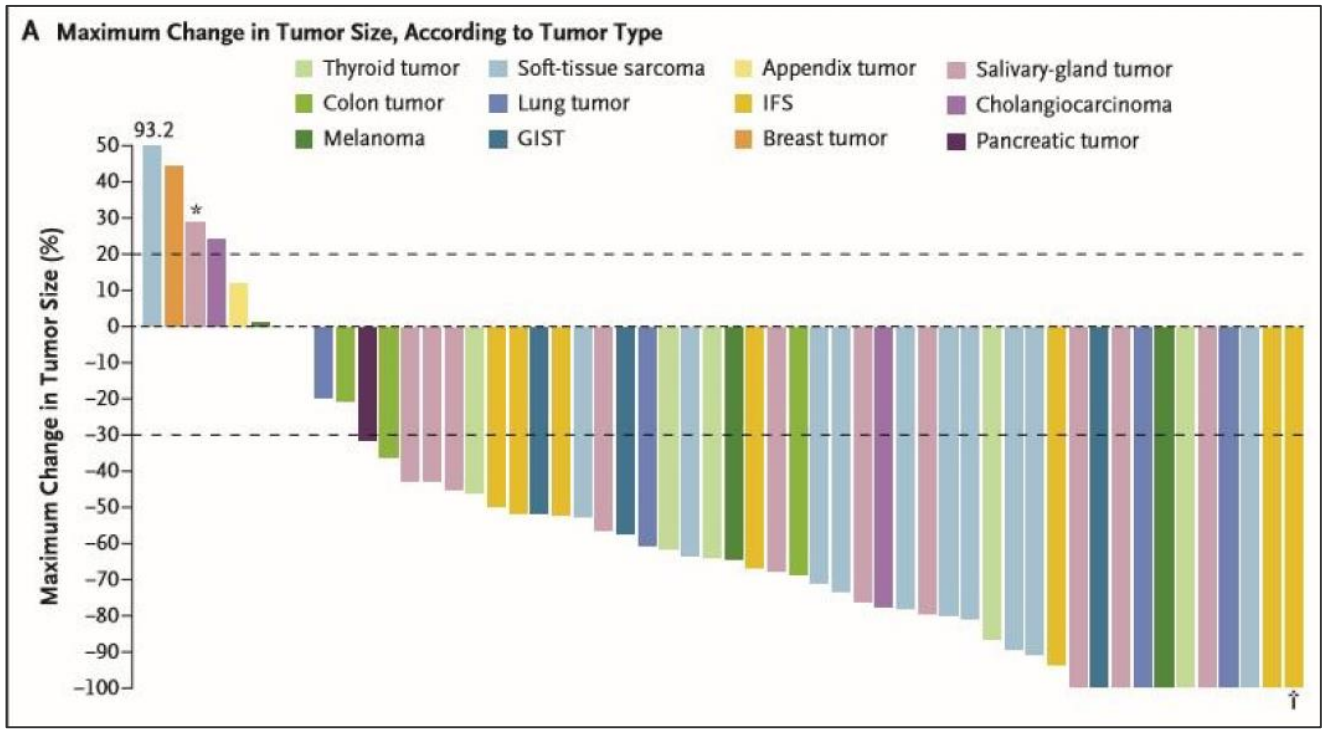


Figure 1 Schematic view of Trk receptors signalling, showing the three major pathways involved in cell differentiation and survival. AKT, v-akt murine thymoma viral oncogene homologue; BDGF, brain-derived growth factor; DAG, diacyl-glycerol; ERK, extracellular signal-regulated kinase; GAB1, GRB2-associated-binding protein 1; GRB2, growth factor receptor-bound protein 2; IP3, inositol trisphosphate; MEK, mitogen-activated protein kinase; NGF, nerve growth factor; NTF-3, neurotrophin 3; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PKC, protein kinase C; PLC, phospholipase C; RAF, rapidly accelerated fibrosarcoma kinase; RAS, rat sarcoma kinase; SHC, Src homology 2 domain containing.

Amatu A, *et al. ESMO Open* 2016;**1**:e000023. doi:10.1136/esmoopen-2015-000023

Larotrectinib: Remarkable Efficacy

(2018, Loxo Oncology)



February 22, 2018
N Engl J Med 2018; 378:731-739
DOI: 10.1056/NEJMoa1714448

- First **new targeted therapy** developed in a tissue type-agnostic manner.
- For patients with TRK fusion cancer, larotrectinib is **a new standard of care**.
- **Routine pan-cancer screening** will be important to identify NTRK fusions.
- **Conclusion**: Larotrectinib demonstrated high antitumor activity regardless of tumor type, age, NTRK mutated gene (1,2 or 3) or NTRK fusion partner.

Newly FDA Approved Agents In 2021

Solid Tumors (10)

- Sotorasiib: NSCLC harboring KRAS G12C gene mutations.
- Tepotinib: Metastatic NSCLC harboring MET exon 14 skipping alterations.
- Mobocertinib: NSCLC harboring EGFR exon 20 insertion mutations.
- Amivantamab-vmjw: Metastatic NSCLC with EGFR exon 20 insertion mutation (a bi-specific antibody)
- Tivozanib: A kinase inhibitor (VEGFR) for renal cell carcinoma (RCC).
- Dostarlimab-gxly: Mismatch repair-deficient (dMMR) endometrial cancer and dMMR advanced solid tumors (Agnostic).
- Infigratinib: Cholangiocarcinoma harboring FGFR2 gene fusion.
- Enfortumab vedotin-ejfv: Antibody-drug conjugate for metastatic urothelial cancer.
- Tisotumab vedotin-tftv: Antibody-drug conjugate for metastatic cervical cancer.
- Belzutifan: A HIF inhibitor for VHL-associated RCC, hemangioblastoma or pNET (Agnostic).

Heme Tumors (5)

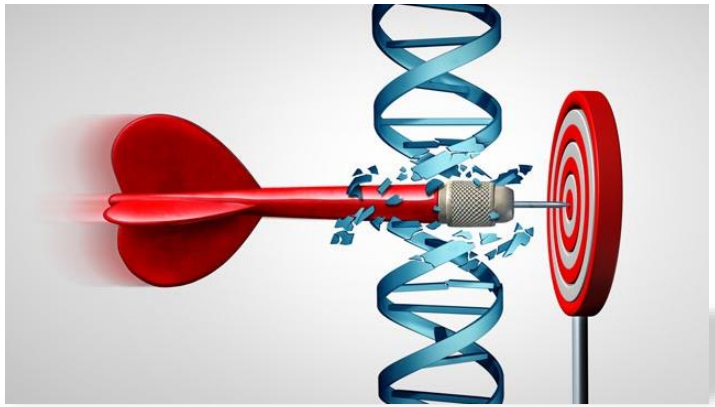
- Liscabtagene maraleucel: Large B-cell lymphoma (CART-T).
- Loncastuximab tesirine-lpyl: Antibody-drug conjugate, large B-cell lymphoma
- Umbralisib: relapsed marginal zone lymphoma (MZL) and follicular lymphoma (FL).
- Melphalan flufenamide: Relapsed multiple myeloma.
- Idecabtagene vicleucel: Relapsed multiple myeloma (CART-T).

PLUS, Over 25 New Indications For Existing Drugs!!!!!!!

- Many Immunotherapy Agents (Atezolizumab, Nivolumab, Pembrolizumab, etc.)
- Ivosidenib: IDH1-mutated cholangiocarcinoma.
- Abemaciclib: First CDK 4/6 inhibitor, adjuvant treatment of breast cancer.

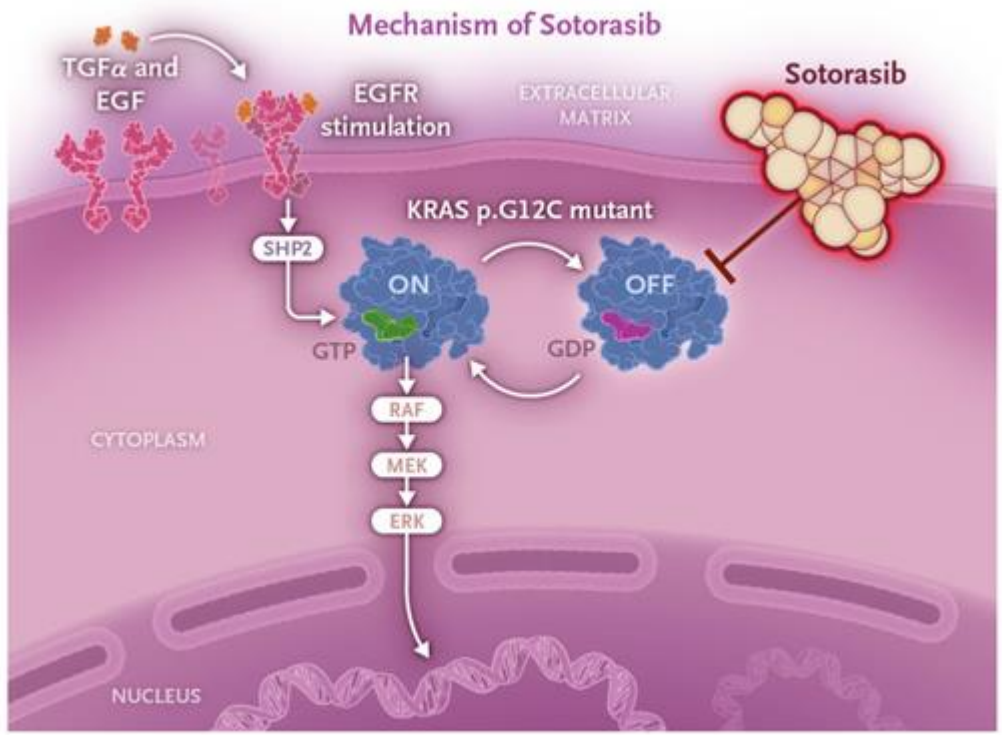
NSCLC Had The Most FDA Approved Agents In 2021

- Sotorasiib: **NSCLC** harboring KRAS G12C gene mutations.
- Tepotinib: Metastatic **NSCLC** harboring MET exon 14 skipping alterations.
- Mobocertinib: **NSCLC** harboring EGFR exon 20 insertion mutations.
- Amivantamab-vmjw: Metastatic **NSCLC** with EGFR exon 20 insertion mutation.



First KRAS^{G12C} Inhibitor Sotorasib (AMG-510)

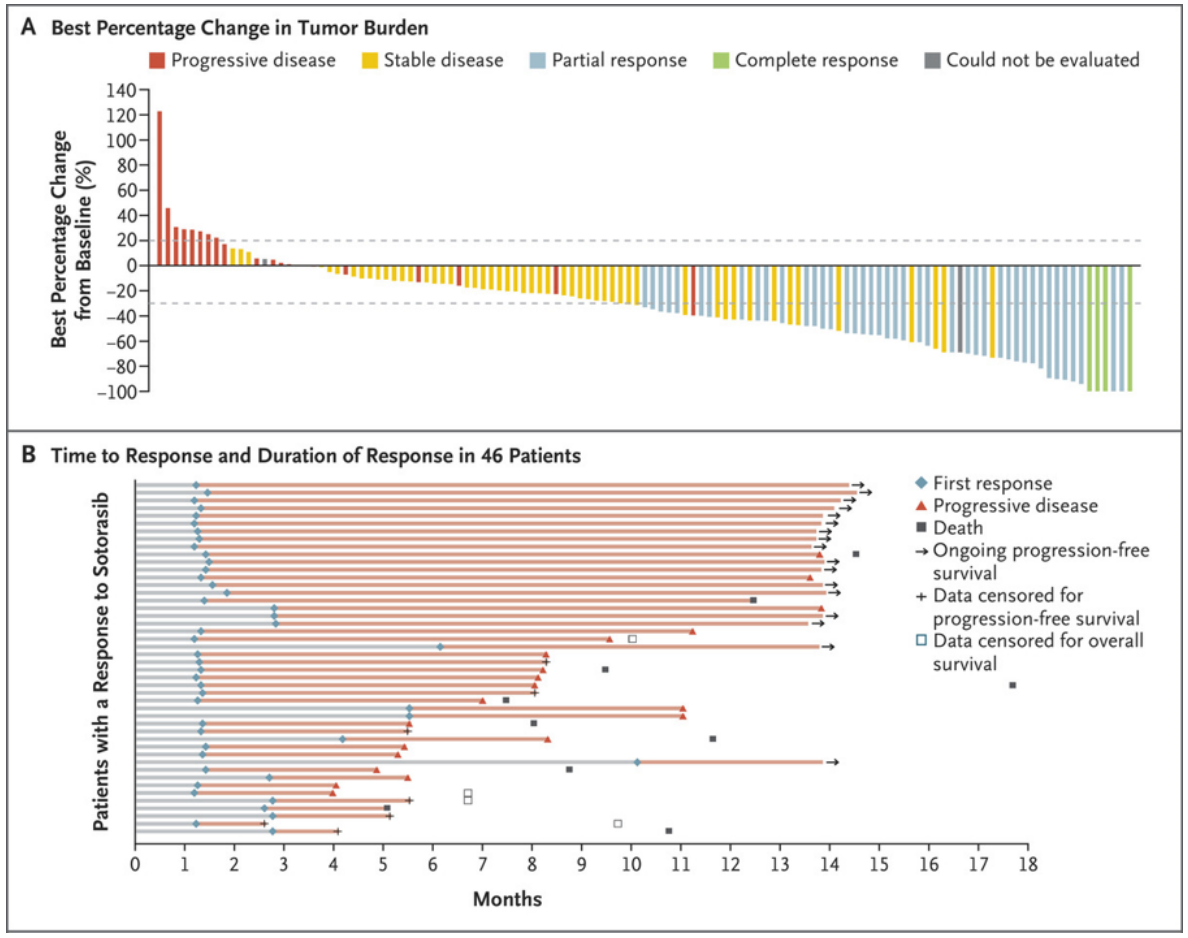
- Accelerated FDA approval on May 28, 2021.
- KRAS G12C seen ~13% NSCLC and ~3% CRC.
- Mutations of KRAS favor the GTP-bound conformational active state and leads to constitutive activation.
- **Sotorasib** is a first-in-class, potent and highly selective small-molecule inhibitor of KRAS G12C that locks it in an inactive GDP-bound state (not active against other KRAS mutant forms).
- Routine testing of KRAS gene is important to identify patients who may benefit from KRAS inhibitors.

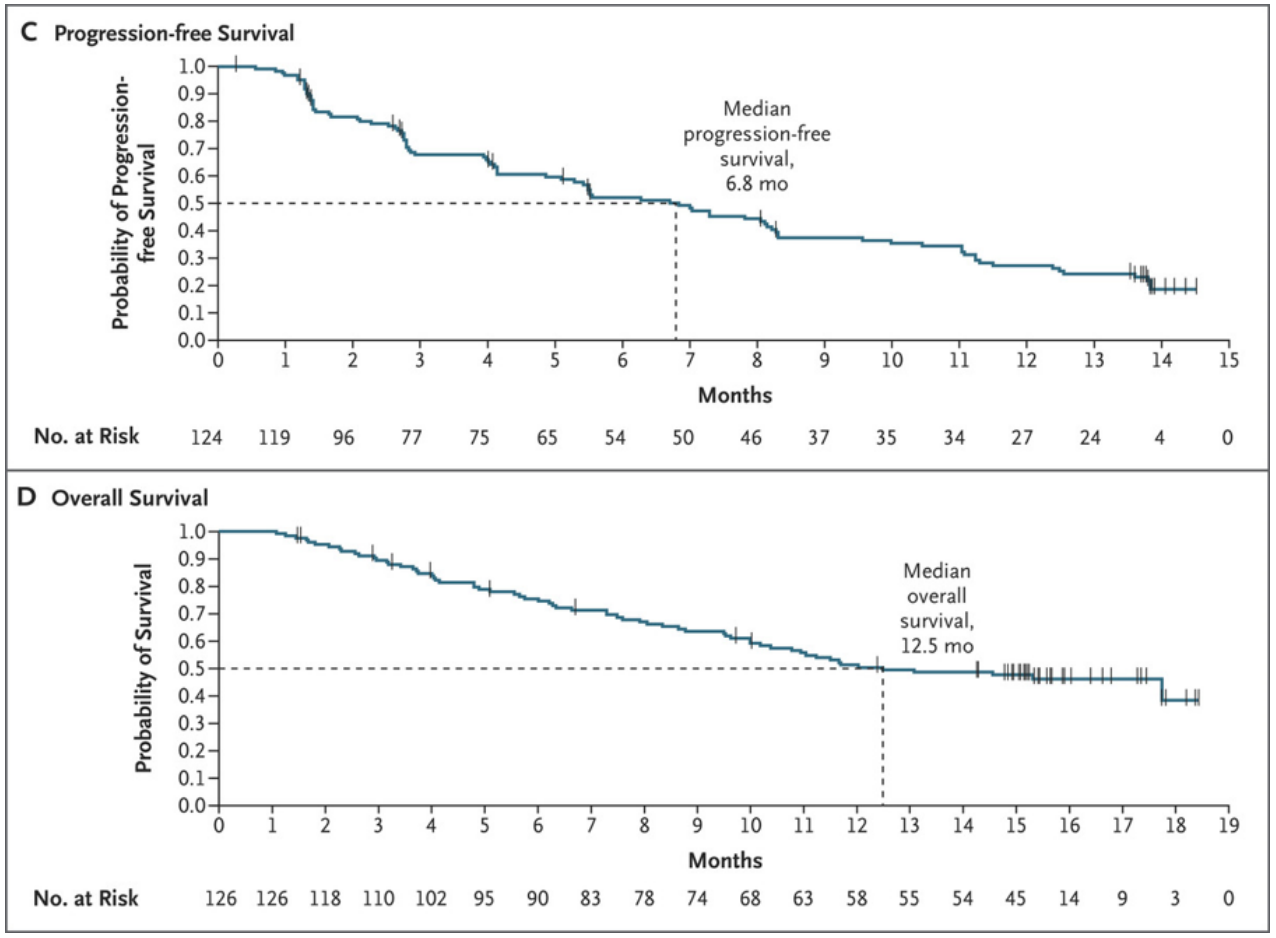


N ENGL J MED 384;25 NEJM.ORG JUNE 24, 2021

NSCLC Patients: Efficacy of Sotorasib Therapy

N ENGL J MED 384;25 NEJM.ORG JUNE 24, 2021





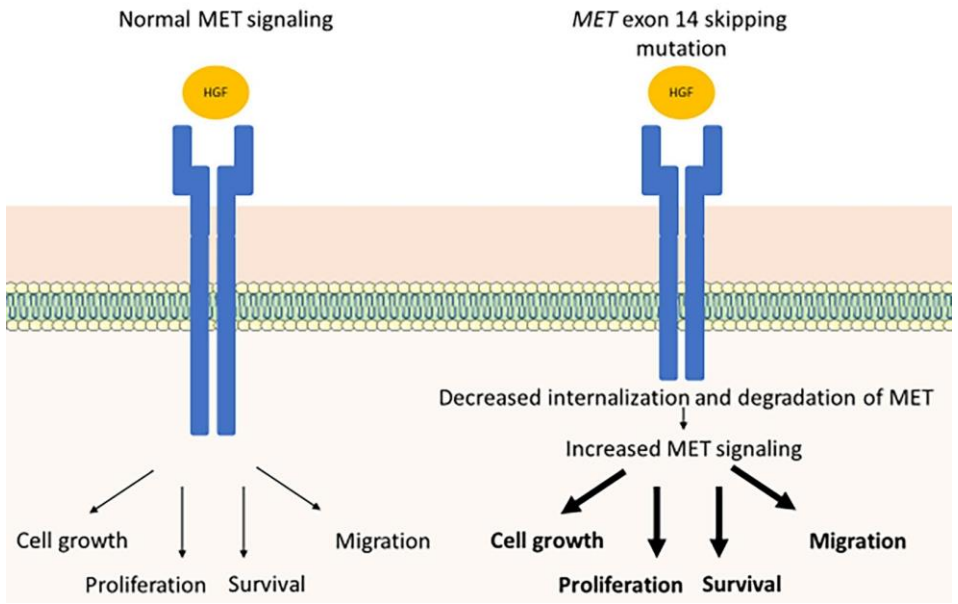
- Overall response rate of ~ 37%, with 80% disease control.
- Duration of response of >11months.

- Median overall survival of 12.5 months in NSCLC.

Tepotinib in NSCLC with MET Exon 14 Skipping Mutations

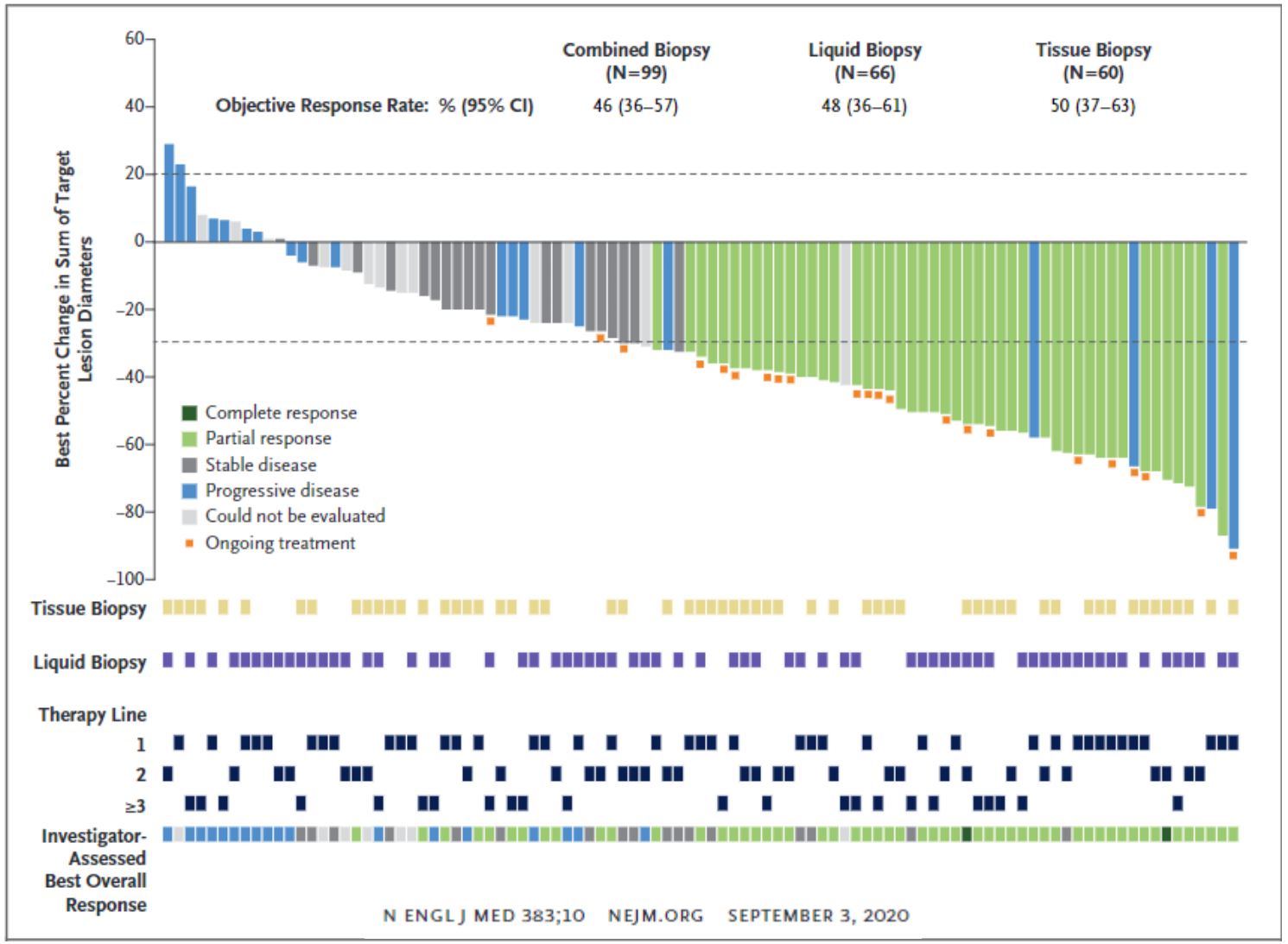
- Accelerated FDA approval (February 2021).
- METex14 skipping mutation, 3-4% of NSCLC.
- These alterations spatially disrupt distinct splicing sites at the acceptor or donor site flanking MET exon 14 which leads to “exon 14 skipping.”
- This leads to impaired MET ubiquitination, decreased MET turnover, and increased signaling.
- Tepotinib showed substantial antitumor activity in approximately half the patients with advanced NSCLC with a MET exon 14 skipping mutation.

Fig. 1 Schematic representation of the effect of *MET*ex14 on MET stability and signaling.



Cancer Treatment Reviews 95 (2021) 102173

Tepotinib in NSCLC with MET Exon 14 Skipping Mutations



- Tepotinib
  - » FDA Approval in 2021
  - » NSCLC with METex14
  - » Response rate was 46%
  - » 11.1 months duration of response
  - » Less side-effect profile
- Capamatinib
  - » FDA Approval in 2020
  - » NSCLC with METex14
  - » Encouraging activity in brain metastasis
- Otherwise, both drugs are similarly efficacious.

First Two EGFR Exon 20 Inhibitors Approved in 2021

Amivantamab

- Previously FDA approved EGFR TKIs have minimal activity for EGFRex20ins-positive mNSCLC.
- Amivantamab is a bi-specific antibody with “2 heads” one targeting EGFR and one MET (RR of 40%).
- Amivantamab has demonstrated preliminary activity in EGFR TKI–resistant tumors driven by EGFR secondary mutations (T790M and/or C797S) or new MET amplification.
- May not penetrate blood-brain-barrier as well as TKIs.
- Adverse events: Infusion reaction.

Journal of Clinical Oncology 39, no. 30 (October 20, 2021) 3391-3402.

Mobocertinib

- Previously FDA approved EGFR TKIs have minimal activity for EGFRex20ins-positive mNSCLC.
- Mobocertinib, a first-in-class, potent, oral, irreversible TKI designed to selectively target in-frame EGFRex20ins mutations in NSCLC (RR of 28%).
- A small molecule irreversible TKI which covalently binds cysteine 797 of EGFR active site.
- C797S-containing mutant can confer resistance to Mobocertinib.
- Adverse events: Gastrointestinal, skin rash, prolongs QTC

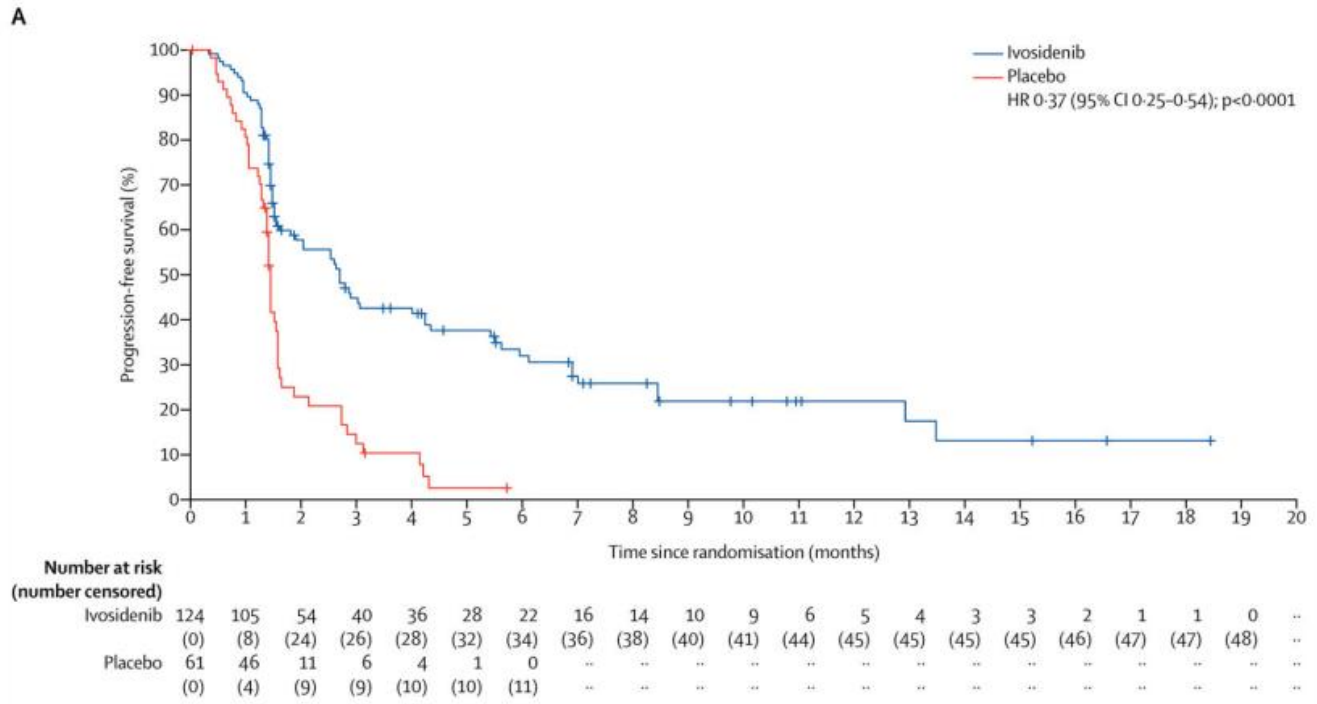
JAMA Oncol. 2021;7(12):e214761. doi:10.1001/jamaoncol.2021.4761.

	1st Generation	2nd Generation	3rd Generation	EGFRex20ins	EGFRex20ins
EGFR TKIs	Gefitinib, Erlotinib	Afatinib, Dacomitinib	Osimertinib	Amivantamab	Mobocertinib
Acquired Resistance	T790M	T790M	C797S	?	C797S

Cells. 2018 Nov; 7(11): 212.

New Indication: Ivosidenib (Tibsovo™) in Cholangiocarcinoma

- IDH1 mutations occur in ~13% of pts with intrahepatic cholangiocarcinoma.
- Ivosidenib targeted inhibitor of mutated IDH1 approved for patients with newly diagnosed acute myeloid leukaemia.
- FDA approved a new indication for Ivosidenib (August 2021).
- PFS was significantly improved with ivosidenib compared with placebo, and ivosidenib was well tolerated.
- This study shows the clinical benefit of targeting IDH1 mutations in advanced, IDH1-mutant cholangiocarcinoma.
- Notable for drug efficacy crossing boundaries between hematologic-solid tumor malignancies (in this case-AML and cholangiocarcinoma).



Lancet Oncol. 2020 June ; 21(6): 796–807. doi:10.1016/S1470-2045(20)30157-1.

First HIF-2α Inhibitor Approval For Cancers Associated with VHL Disease

- Von Hippel-Lindau Syndrome is a hereditary cancer syndrome characterized by the development of multiple vascular tumors.
- Inactivation of VHL leads to aberrant stabilization and accumulation of HIF-2α, which drives tumor growth.
- **Belzutifan** is a first-in-class FDA-approved HIF-2α inhibitor for VHL-associated RCC, hemangioblastoma or pNET.
- Belzutifan prevents heterodimerization of HIF-2α and downstream activation of transcription.
- Example of agnostic FDA approval.

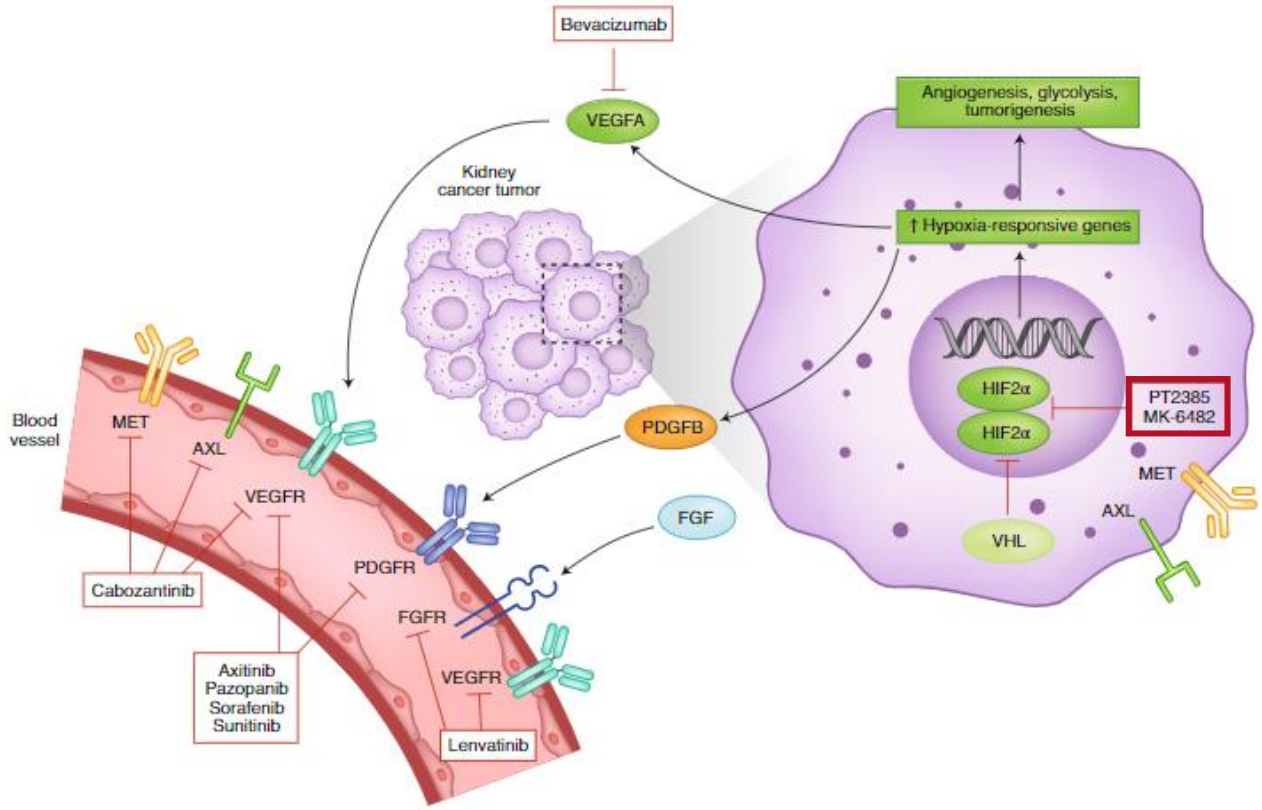
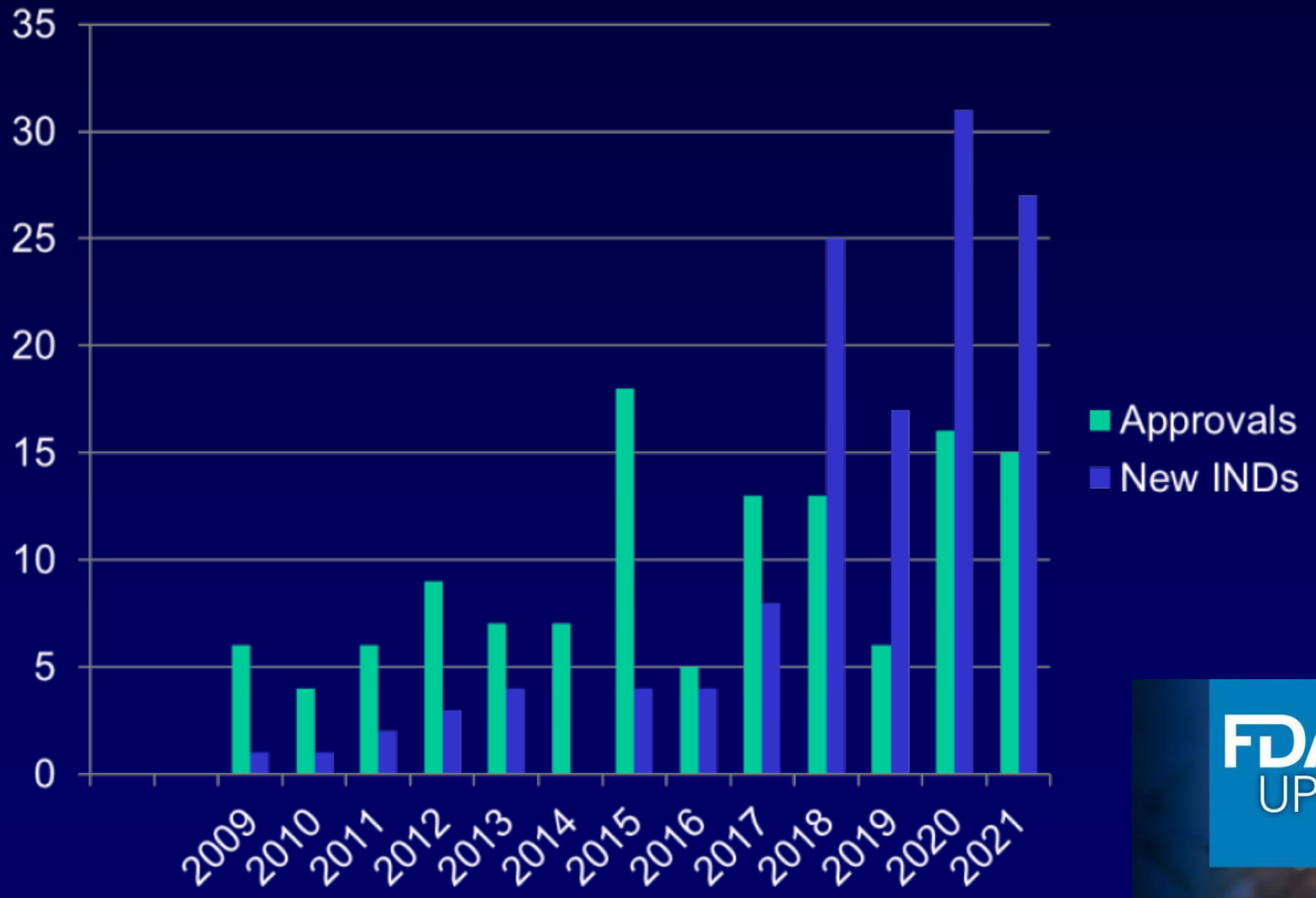


Fig. 1 | HIF-2α inhibitors as novel inhibitors of the HIF2–VEGF–VEGFR pathway.

NATURE MEDICINE | VOL 26 | OCTOBER 2020 | 1519–1530 | www.nature.com/naturemedicine

Trends in New Drug Approval



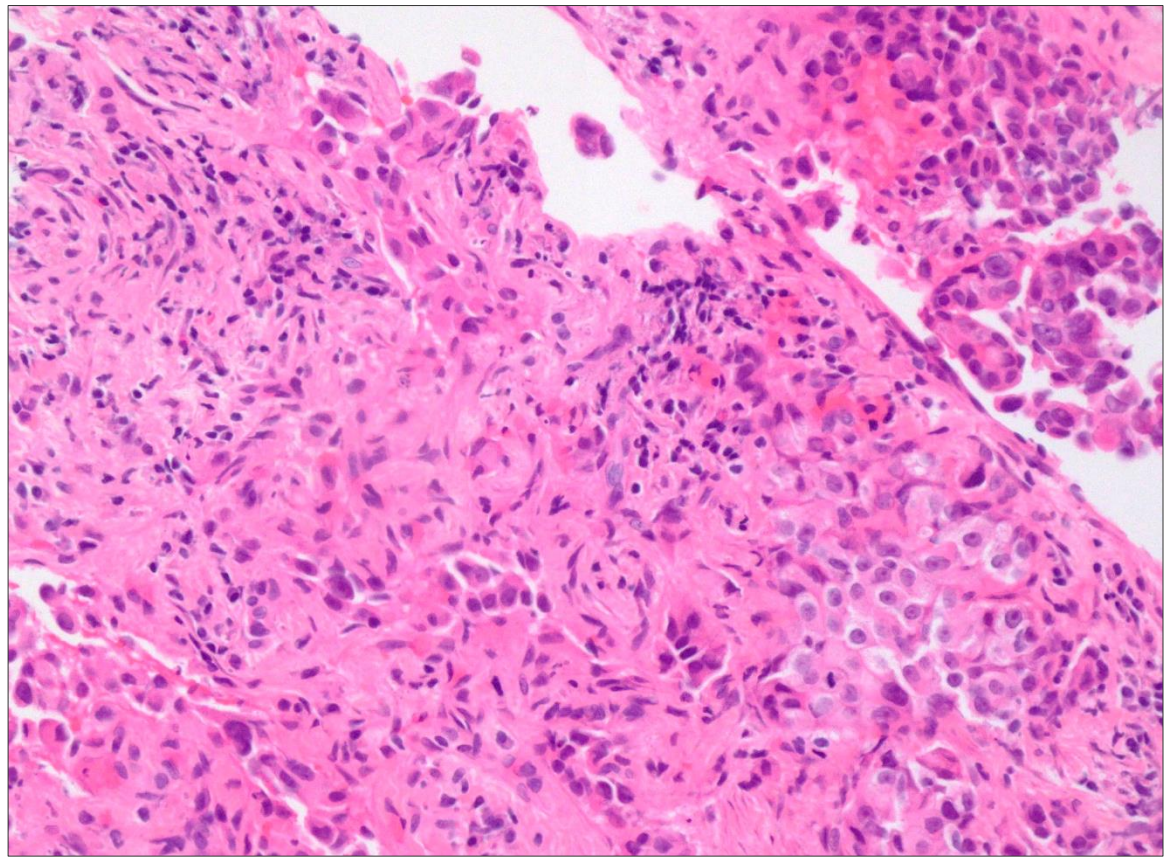
Learning Objectives

1. Understand Comprehensive Genomic Profiling By NGS Testing.
2. Understand How Molecular Tumor Board Can Support Precision Oncology.
3. Review Newly FDA-Approved Oncologic Therapies In 2021.
4. A Case Study In Precision Oncology: NSCLC Patient With Brain Metastasis.

Case: 49-year-old male, Stage-4 NSCLC

- March 2019- Chief complaint of cough (OSH)
- CT- pulmonary mass, LAD
- MRI- Mets to brain and axial skeleton
- Biopsy- Invasive moderately differentiated adenocarcinoma with squamoid features
- Neg EGFR (Sanger), Neg BRAF (PCR)
- ALK and ROS1 FISH: N/A
- PD-L1: 80%

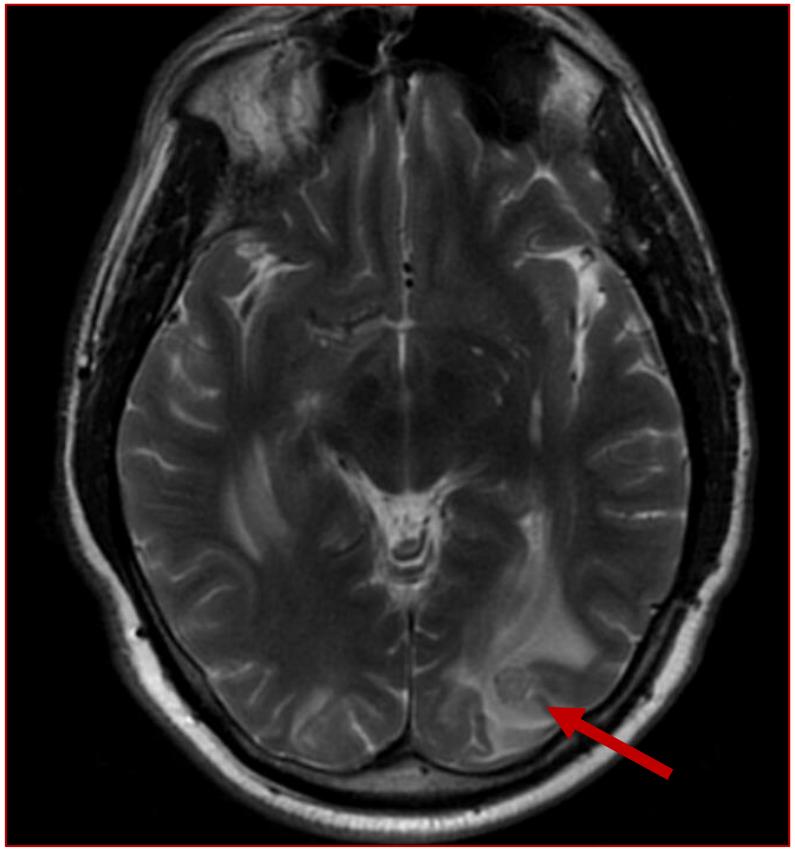
- April 2019- Referred to Tertiary Academic Hospital
- Supraclavicular LN Biopsy
- NGS tumor profiling (DNA/RNA)

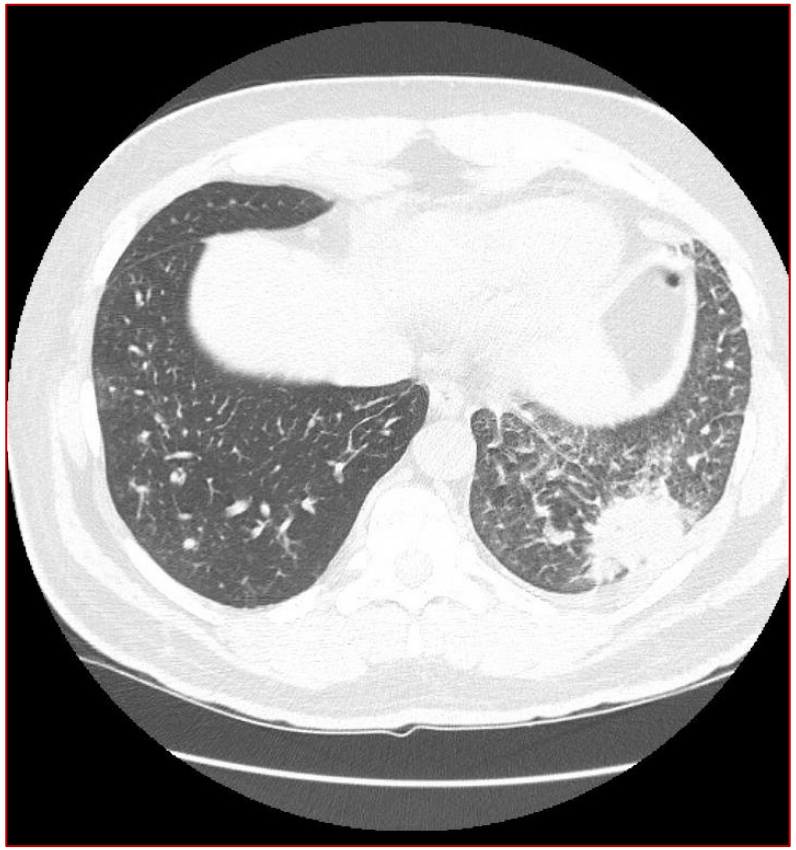


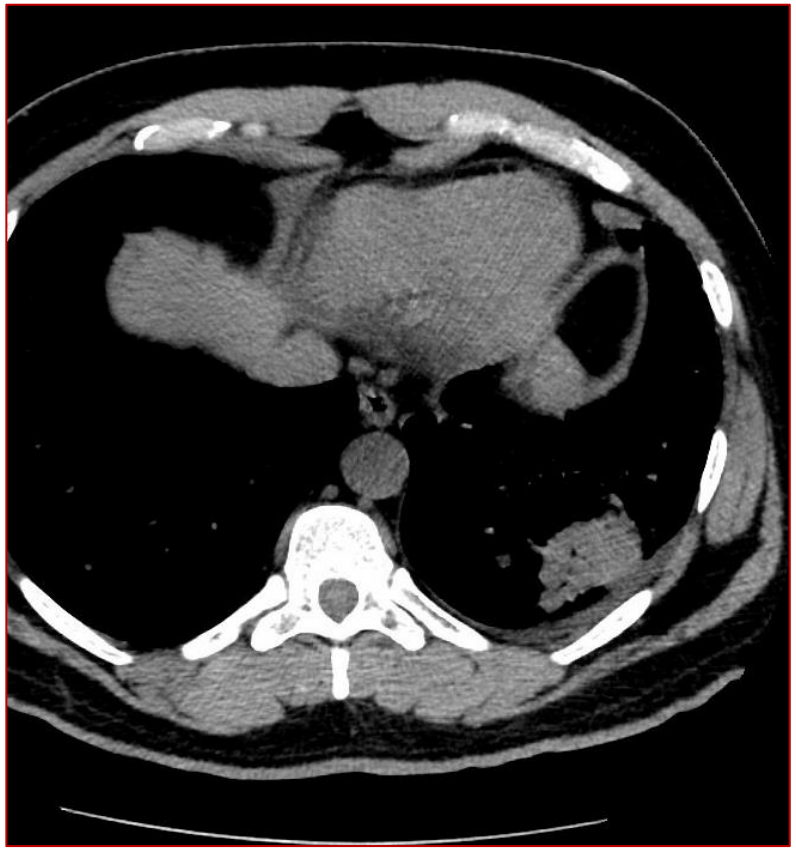
Supraclavicular LN Biopsy

JCO Precis Oncol. 2021 Nov;5:88-92. doi: 10.1200/PO.20.00296.

MRI and CT on March 2019

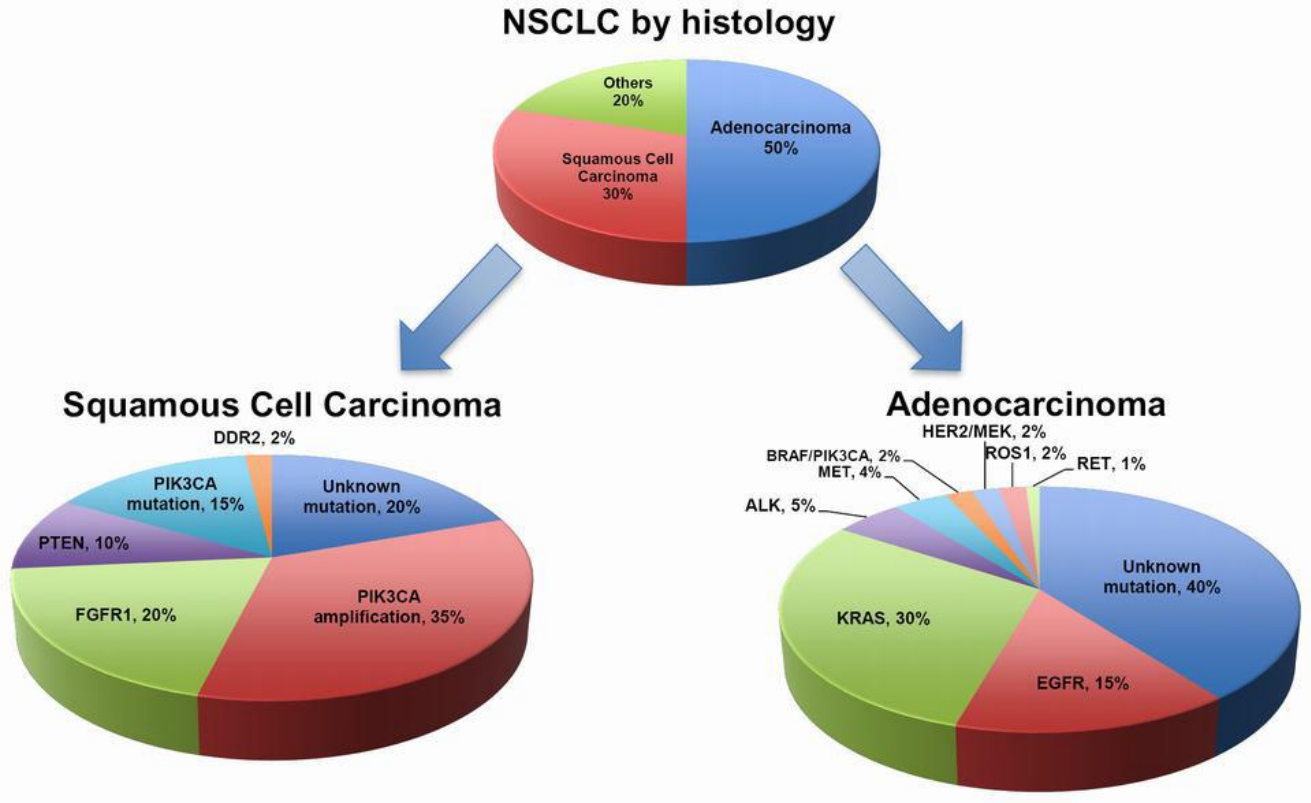


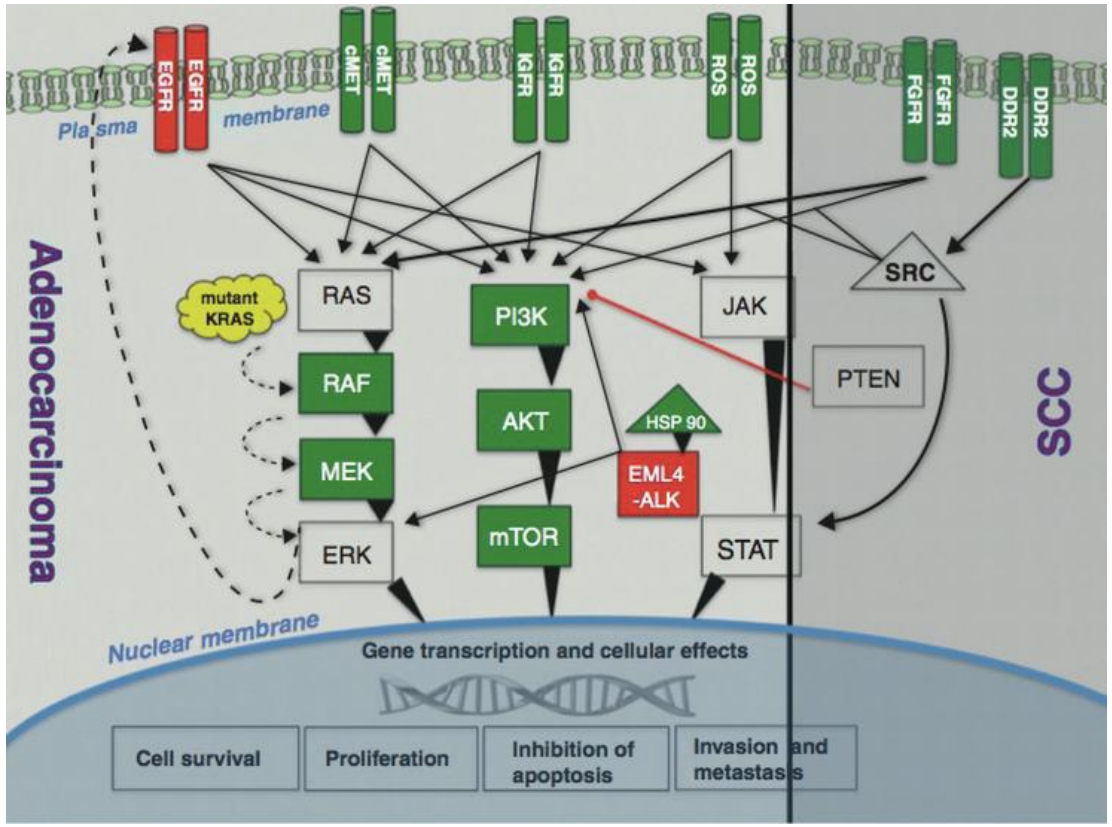




JCO Precis Oncol. 2021 Nov;5:88-92. doi: 10.1200/PO.20.00296.

NSCLC Mutational Landscape and Pathways





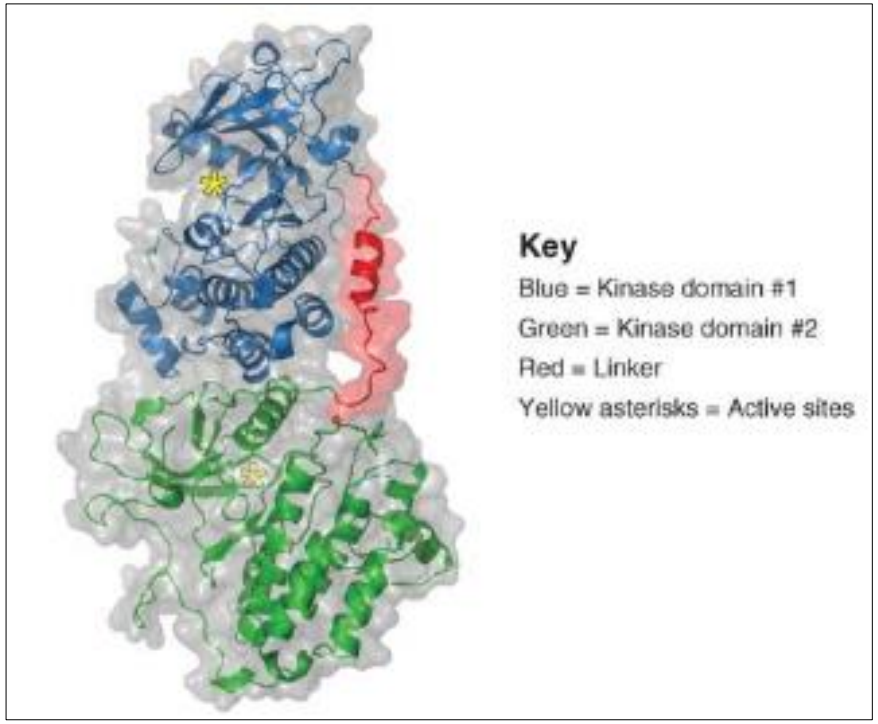
• Vol 4, No 1 (February 2015) Targeted therapy for non-small cell lung cancer: current standards and the promise of the future

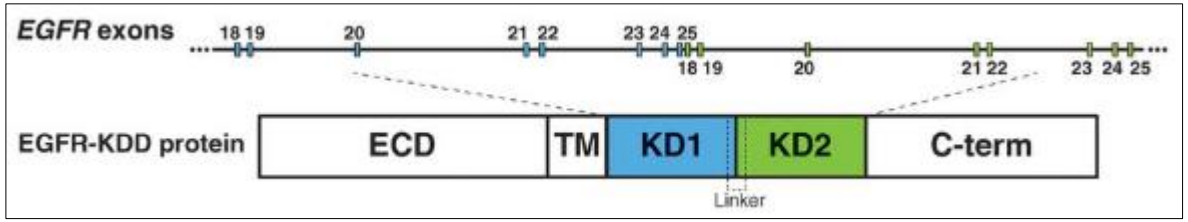
Comprehensive NGS Tumor Profiling* (April 2019)

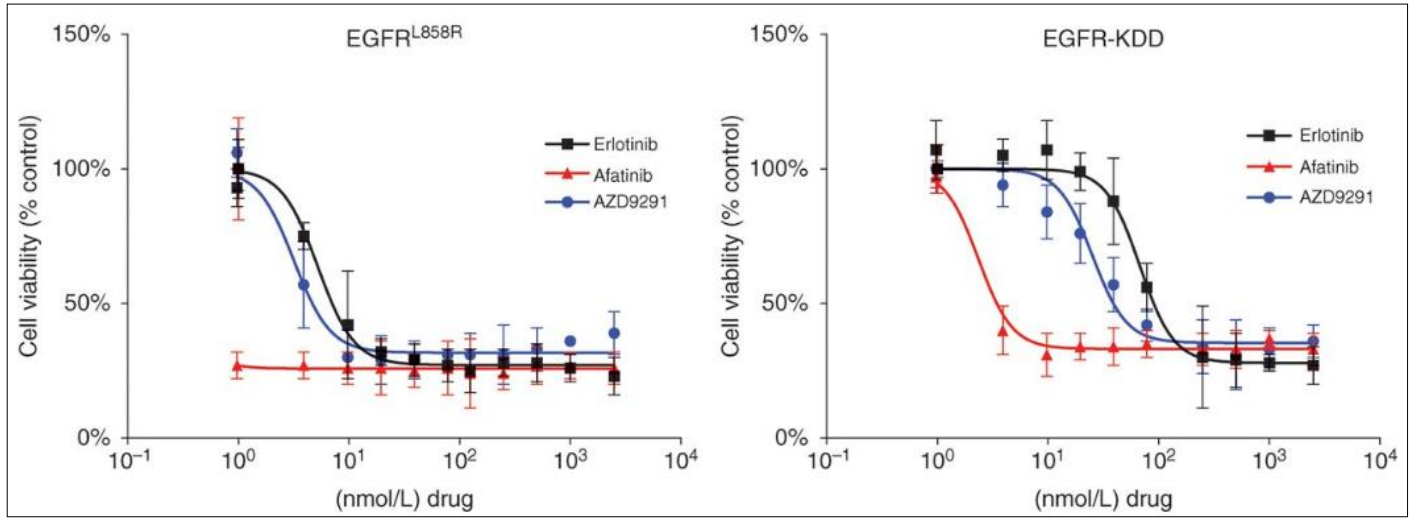
RESULT SUMMARY						
Variant Detected	FDA Approved Therapy Within Indication	FDA Approved Therapy Outside Indication	Resistance to Therapies	NCCN Guidelines	Clinical Trial Opportunity	TMB
EGFR Exon 18 to 25 Kinase Domain Duplication	Osimertinib, Erlotinib, Afatinib, Gefitinib	No	No	Yes - see variant details below	Yes - see below	3 Muts/Mb

*161 Gene Panel: SNVs, Indels, CNV, Fusions

EGFR Kinase Domain Duplication







https://cancerdiscovery.aacrjournals.org/content/5/11/1155

AZD9291 (Osimertinib)

- **March 2019**- Chief complaint of cough (OSH)
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- MRI- Mets to brain and axial skeleton
- Biopsy- Invasive moderately differentiated adenocarcinoma with squamoid features
- Neg EGFR (Sanger), Neg BRAF (PCR)
- ALK and ROS1 FISH: N/A
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- **April 2019**- Referred to Tertiary Academic Hospital
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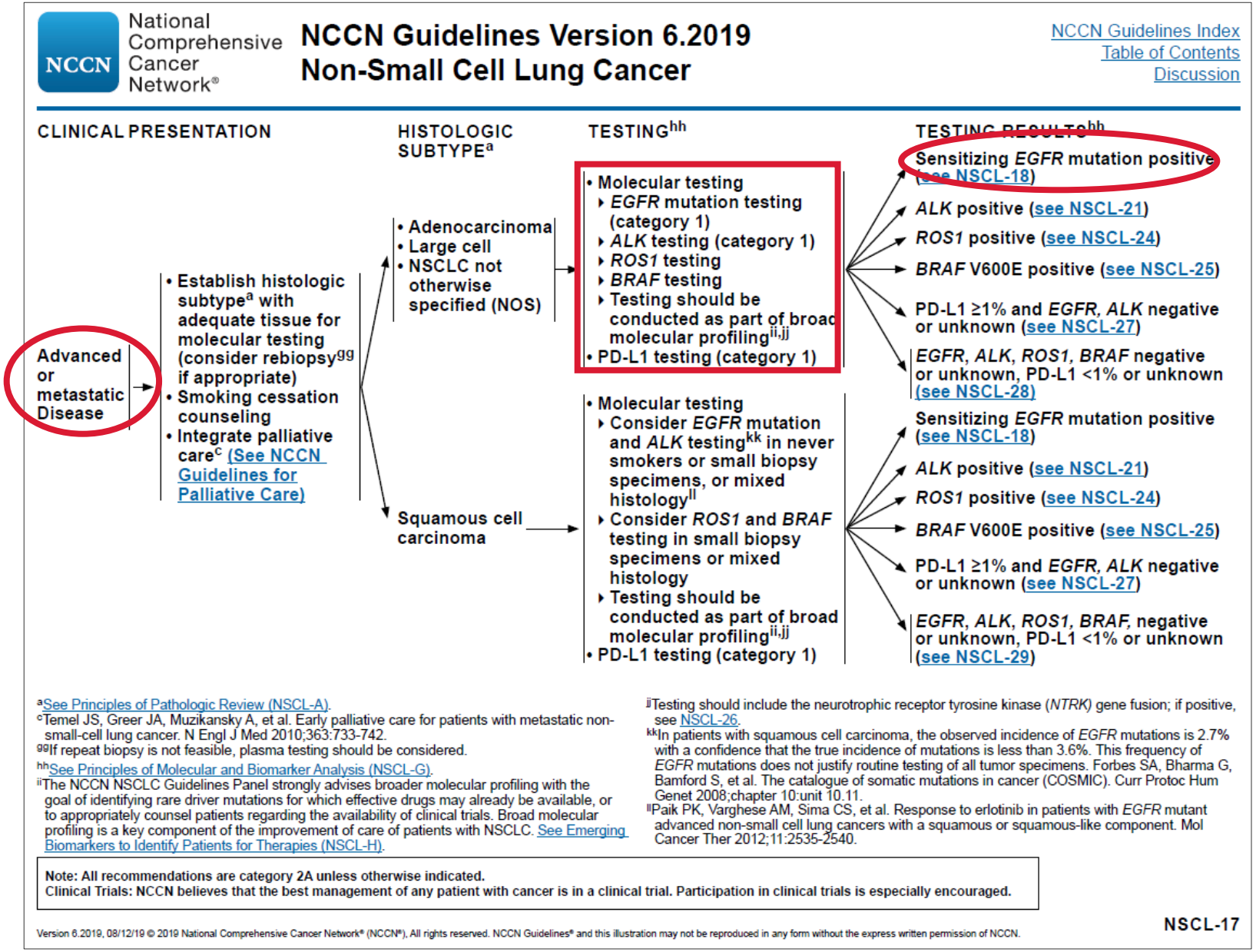
- NGS tumor profiling (DNA/RNA)
- EGFR Kinase Domain Duplication

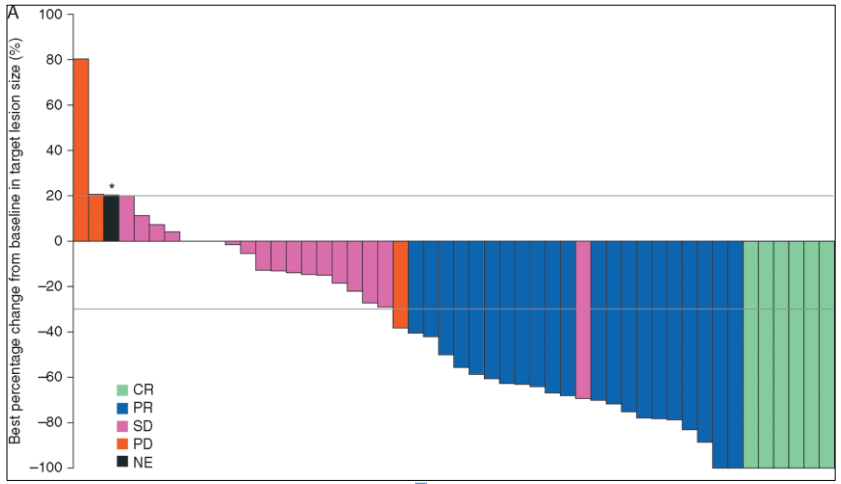


Pooled Analysis of 2 Phase II Studies

Annals of Oncology, Volume 29, Issue 3, March 2018, Pages 687–693

Central nervous system response to osimertinib

Patients evaluable for CNS response ($n = 50$)	
CNS ORR[a], (95% CI)	54% (39% to 68%)
Complete response, *n* (%)	6 (12)
Partial response, *n* (%)	21 (42)
Stable disease ≥6 weeks, *n* (%)	19 (38)
Progressive disease, *n* (%)	3 (6)
Not evaluable, *n* (%)	1 (2)



Patient Started on Tagrisso 80 mg daily (April 2019).

National Comprehensive Cancer Network®

NCCN Guidelines Version 6.2019
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SENSITIZING EGFR MUTATION POSITIVE[hh]

FIRST-LINE THERAPY[mm]

Sensitizing *EGFR* mutation positive

***EGFR* mutation discovered prior to first-line systemic therapy**

- Osimertinib[nn] (category 1) (preferred) → Progression → See Subsequent Therapy (NSCL-20)
- Erlotinib[nn] (category 1) or Afatinib[nn] (category 1) or Gefitinib[nn] (category 1) or Dacomitinib[nn] (category 1) → Progression → See Subsequent Therapy (NSCL-19)

***EGFR* mutation discovered during first-line systemic therapy**

Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by osimertinib (preferred) or erlotinib or afatinib or gefitinib or dacomitinib

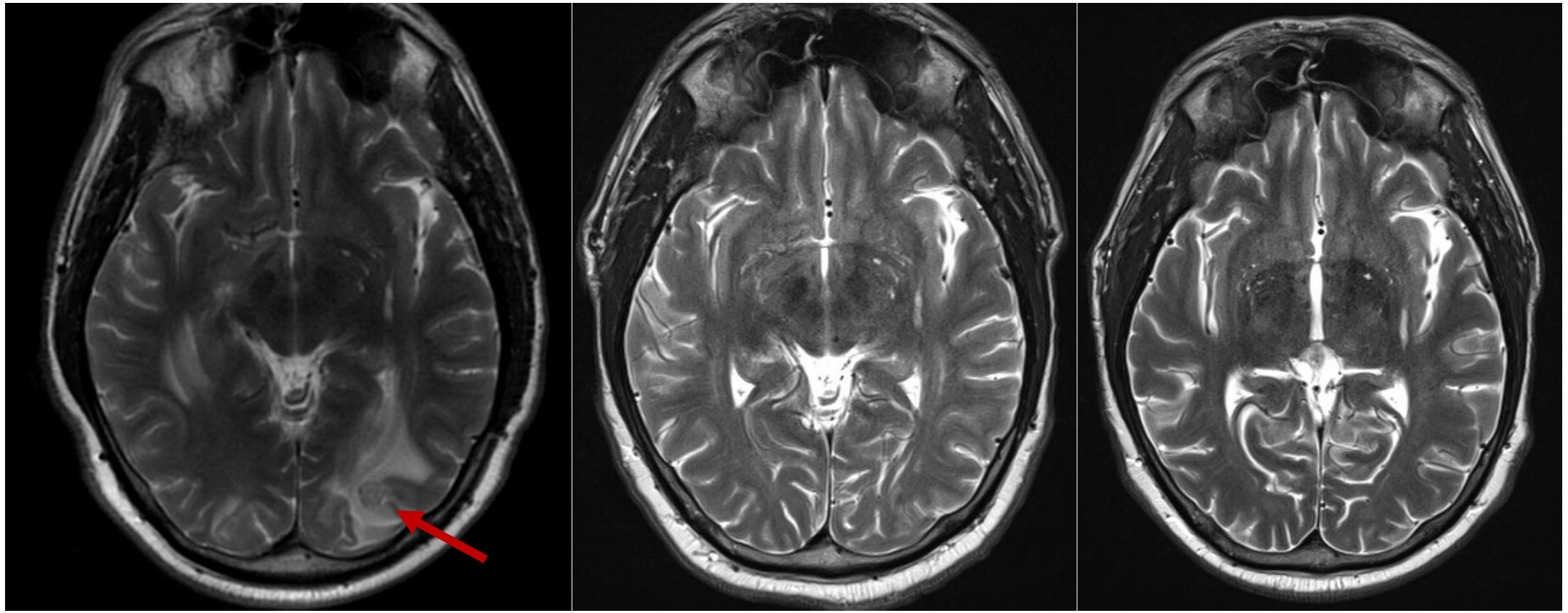
- → Progression → See Subsequent Therapy (NSCL-20)
- → Progression → See Subsequent Therapy (NSCL-19)

[hh]See Principles of Molecular and Biomarker Analysis (NSCL-G).
[mm]See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[nn]For performance status 0-4.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NSCL-18

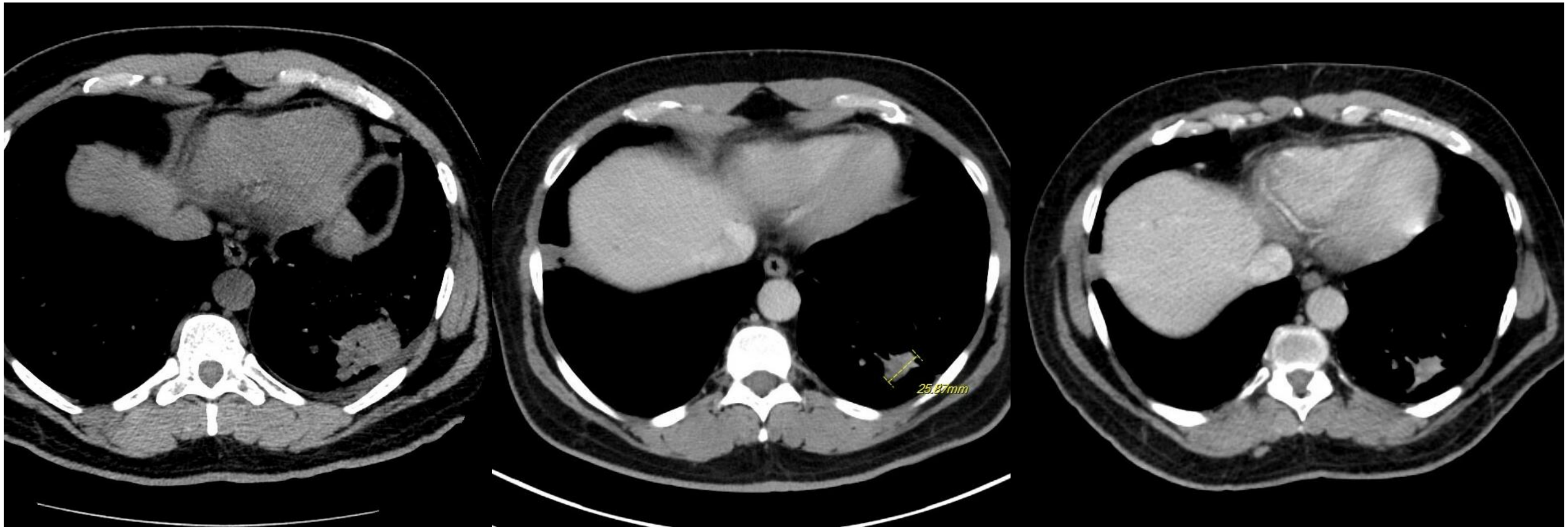
Brain: Repeat Imaging



March 2019 **August 2019** **May 2020**

JCO Precis Oncol. 2021 Nov;5:88-92. doi: 10.1200/PO.20.00296.

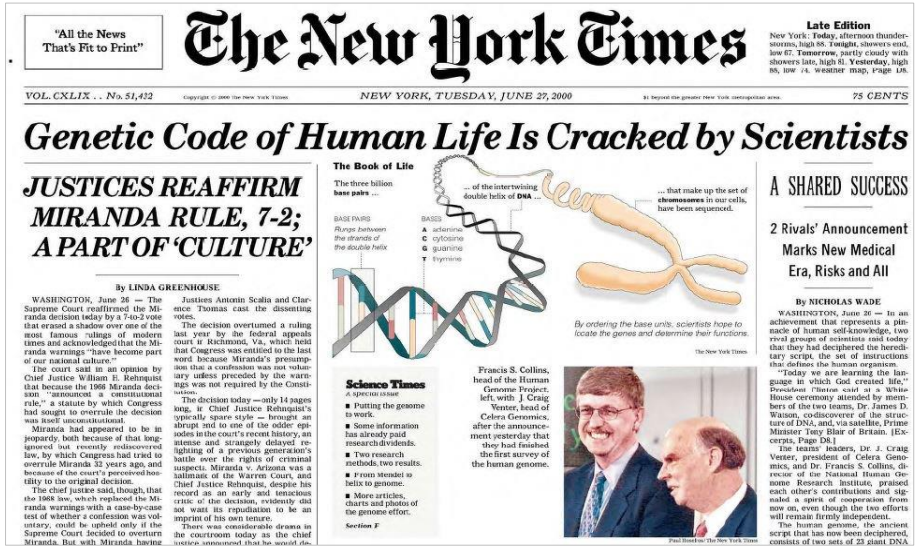
Lung: Repeat Imaging



March 2019 **August 2019** **September 2019**

JCO Precis Oncol. 2021 Nov;5:88-92. doi: 10.1200/PO.20.00296.

Past



"All the News That's Fit to Print"

The New York Times

Late Edition

VOL. CXLIX . . No. 51,422 NEW YORK, TUESDAY, JUNE 27, 2000 75 CENTS

Genetic Code of Human Life Is Cracked by Scientists

JUSTICES REAFFIRM MIRANDA RULE, 7-2; A PART OF 'CULTURE'

By LINDA GREENHOUSE

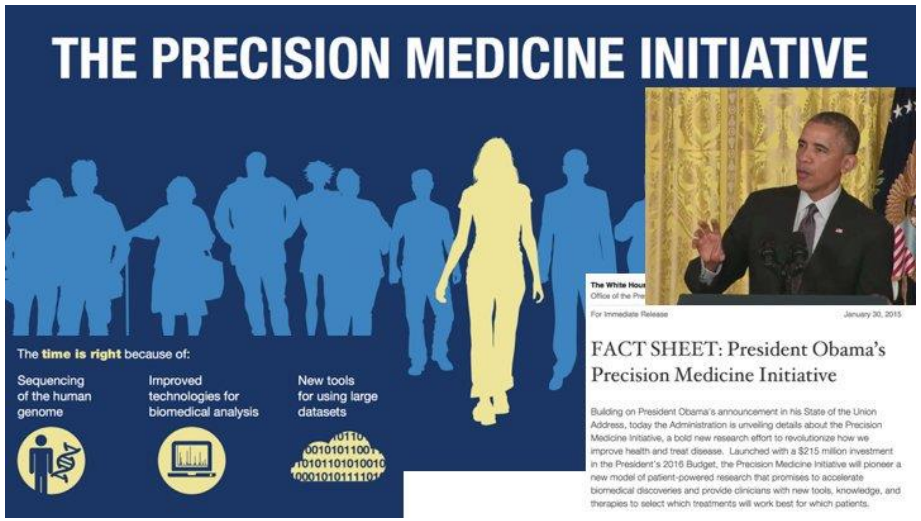
The Book of Life

Science Times

A SHARED SUCCESS

2 Rivals' Announcement Marks New Medical Era, Risks and All

By NICHOLAS WADE



THE PRECISION MEDICINE INITIATIVE

The time is right because of:

Sequencing of the human genome

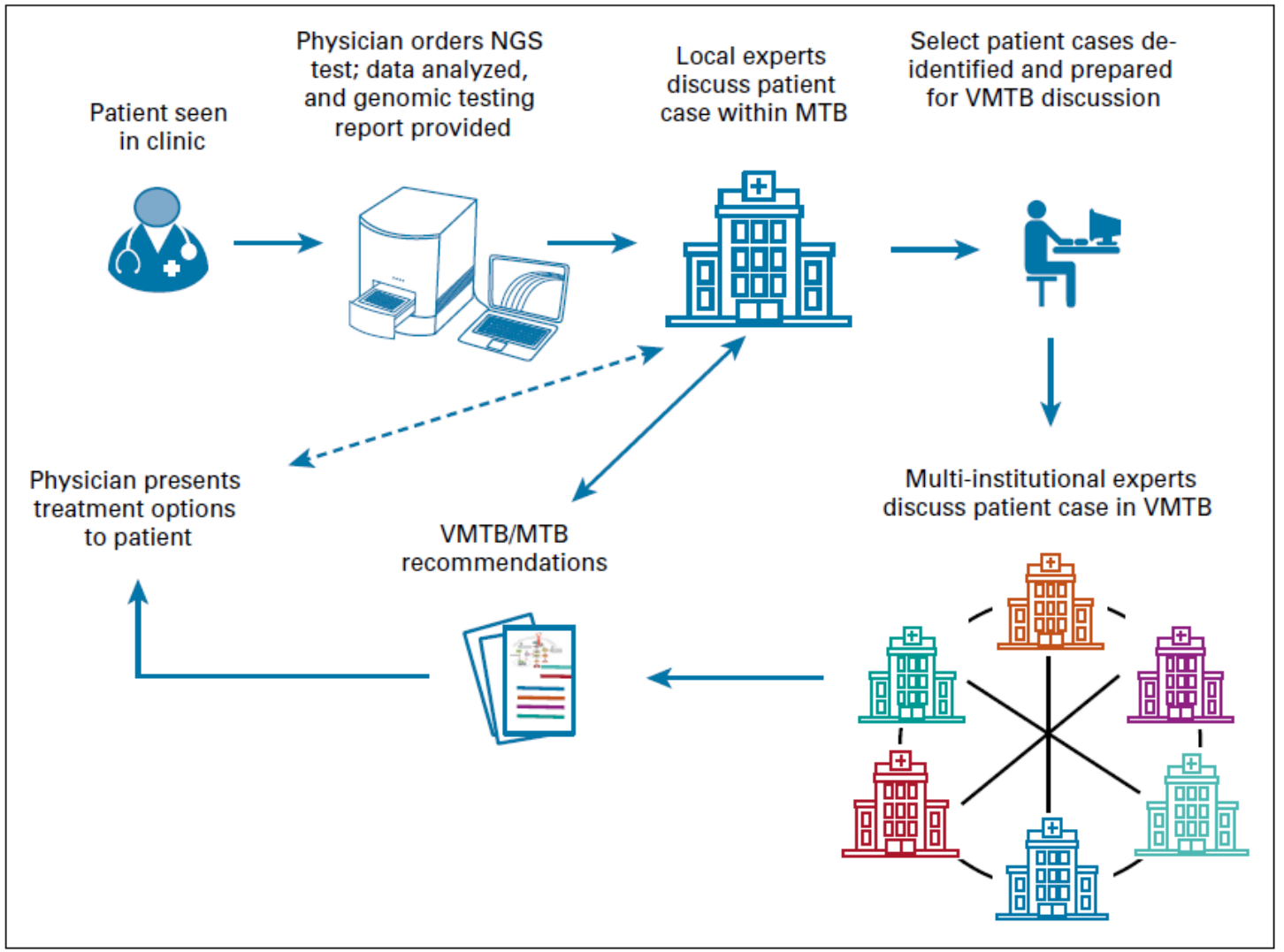
Improved technologies for biomedical analysis

New tools for using large datasets

FACT SHEET: President Obama's Precision Medicine Initiative

Building on President Obama's announcement in his State of the Union Address, today the Administration is unveiling details about the Precision Medicine Initiative, a bold new research effort to revolutionize how we improve health and treat disease. Launched with a $215 million investment in the President's 2016 Budget, the Precision Medicine Initiative will pioneer a new model of patient-powered research that promises to accelerate biomedical discoveries and provide clinicians with new tools, knowledge, and therapies to select which treatments will work best for which patients.

Present and Future



Thank You: Any Questions?

ARUP is a nonprofit enterprise of the University of Utah and its Department of Pathology.