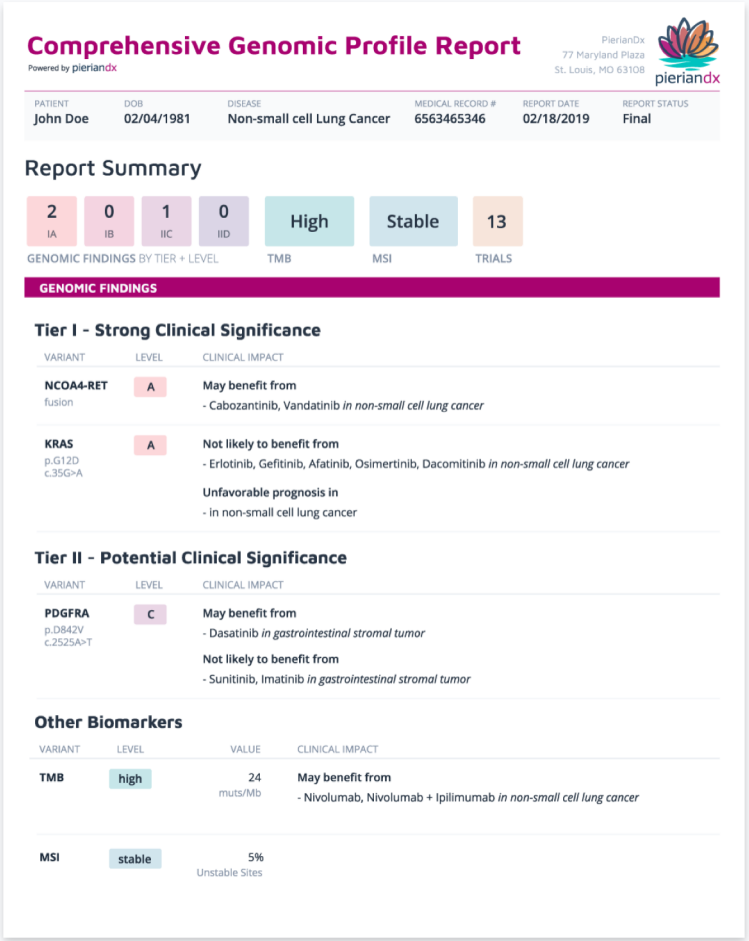


Comprehensive Genomic Profile Report

Powered by pierianDx

PierianDx
77 Maryland Plaza
St. Louis, MO 63108

pierianDx

PATIENT	DOB	DISEASE	MEDICAL RECORD #	REPORT DATE	REPORT STATUS
John Doe	02/04/1981	Non-small cell Lung Cancer	6563465346	02/18/2019	Final

Report Summary

2 IA	0 IB	1 IIC	0 IID	High	Stable	13
GENOMIC FINDINGS BY TIER + LEVEL				TMB	MSI	TRIALS

GENOMIC FINDINGS

Tier I - Strong Clinical Significance

VARIANT	LEVEL	CLINICAL IMPACT
NCOA4-RET fusion	A	**May benefit from** - Cabozantinib, Vandatinib *in non-small cell lung cancer*
KRAS p.G12D c.35G>A	A	**Not likely to benefit from** - Erlotinib, Gefitinib, Afatinib, Osimertinib, Dacomitinib *in non-small cell lung cancer* **Unfavorable prognosis in** - in non-small cell lung cancer

Tier II - Potential Clinical Significance

VARIANT	LEVEL	CLINICAL IMPACT
PDGFRA p.D842V c.2525A>T	C	**May benefit from** - Dasatinib *in gastrointestinal stromal tumor* **Not likely to benefit from** - Sunitinib, Imatinib *in gastrointestinal stromal tumor*

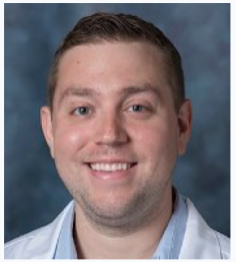
Other Biomarkers

VARIANT	LEVEL	VALUE	CLINICAL IMPACT
TMB	high	24 muts/Mb	**May benefit from** - Nivolumab, Nivolumab + Ipilimumab *in non-small cell lung cancer*
MSI	stable	5% Unstable Sites	

pieriandx

Report Optimization: Maximizing the Clinical Utility of Next Generation Sequencing

Eric Vail, MD
Director, Molecular Pathology
Cedars-Sinai Medical Center



Rakesh Nagarajan, MD, PhD
Executive Chairman and Founder
PierianDx

Moderated by: OncLive

Agenda

1. **The Evolving Landscape of Precision Medicine and Oncology Testing**
   Rakesh Nagarajan, MD, PhD - PierianDx

2. **The Utility and Associated Challenges of Genomic Profiling**
   Eric Vail, MD - Cedars-Sinai Medical Center

3. **Optimizing Clinical Utility & Value of Genomic Reporting**
   Eric Vail, MD - Cedars-Sinai Medical Center

4. **Q&A**
   Eric Vail, MD and Rakesh Nagarajan, MD, PhD

Rapid Rise of Precision Medicine

Numbers and Milestones

284 Total # of FDA approved pharmacogenomic biomarkers; 108 in oncology[1]

25 Personalized medicine approvals in 2018 (42% of NMEs)[2]

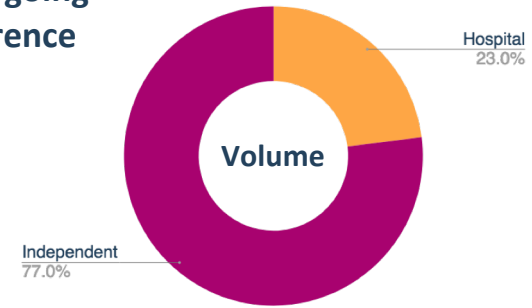
10 Cancer-related personalized medicine approvals in 2018[2]

2nd Approval of a cancer drug (Vitrakvi) indication based on biomarker, not tumor type[2]

3/16/18 CMS announces national coverage policy for NGS diagnostics

Hospitals billing for comprehensive genomic profiling (CGP)[3]

Most of the CGP volume is going to a few independent reference labs.[3]



Sources:
1. FDA - Table of Pharmacogenomic Biomarkers in Drug Labeling. Data as of June 2018
2. Personalized Medicine at FDA: A Progress & Outlook Report, Personalized Medicine Coalition, 2018.
3. Boston Healthcare Associates analysis of claims data 2016.

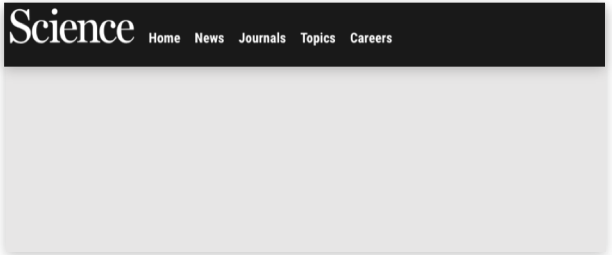
Recent Trends

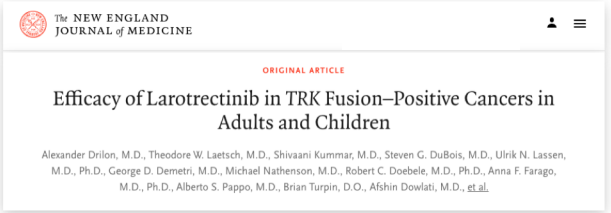
Biomarker and NGS Testing

Biomarker Testing	NGS Testing
Progressive increase in oncology due to tumor agnostic biomarkers developed to inform targeted and immune therapies	More laboratories performing NGS for common tumor types with approved therapies
Standardized testing algorithms drive biomarker testing for common tumors (NSCLC, CRC, breast) at diagnosis at many healthcare settings	**Tumor agnostic** markers, such as MSI, TMB, and NTRK fusions are significant driver of more NGS testing
	Improving payor coverage with recent Medicare coverage for FDA-approved NGS tests

Approved

Microsatellite Instability, NTRK Fusions





Emerging

Tumor Mutational Burden

Single-marker, Tumor-specific to Comprehensive Genomic Profiling

Oncology Testing is Evolving

Current → **Near-Term** → **Long-Term**

Single Markers and Hotspot Panels

Specific patient populations are tested for specific biomarkers using conventional methods (e.g., EGFR PCR for NSCLC)

Limits on tissue availability make this approach less sustainable long-term

Broad NGS Testing

NGS / CGP increasingly dominates conventional methods (e.g., PCR, FISH)

Use of a single test on a single sample to obtain a comprehensive biomarker status of the patient

Multi-Modality

Mix of test methods gives best picture

Possible reflex test patterns with some tests being prioritized because of their ease of use/affordable cost

Some FDA approved; some LDTs

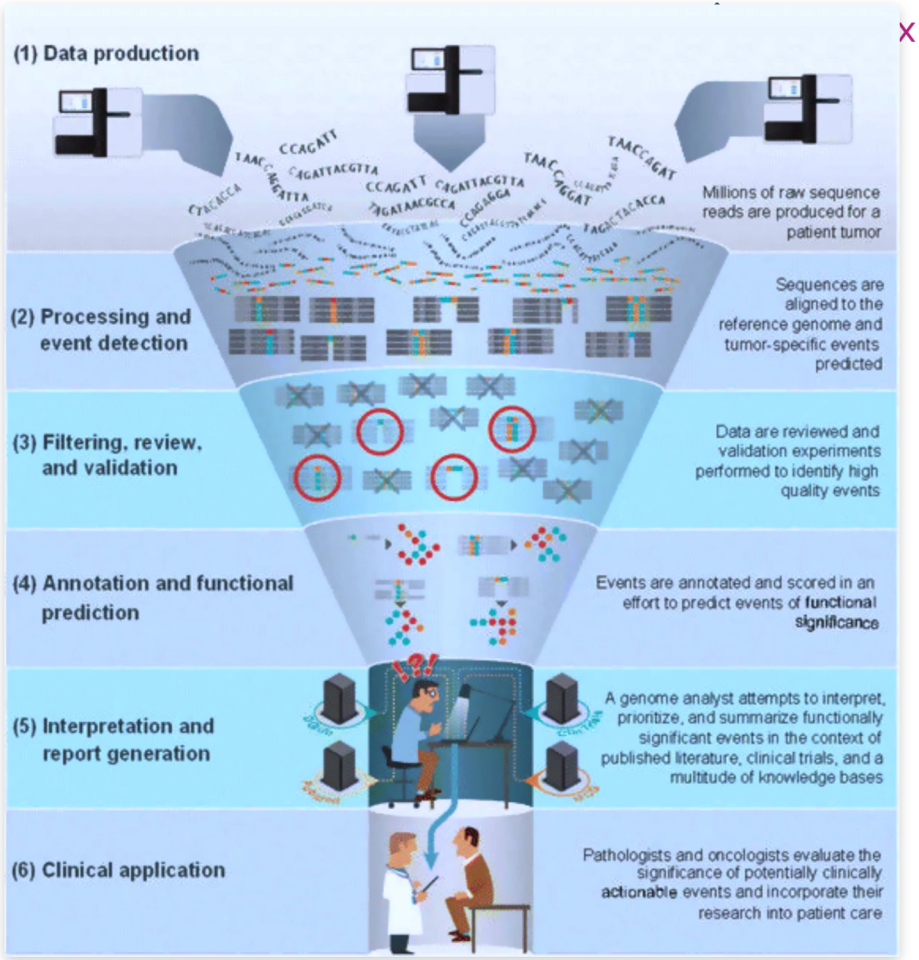
Informatics deployed to create genotypic and phenotypic profile of patient

Source: Boston Healthcare Analysis

In-House NGS Testing

Overcoming the Challenges

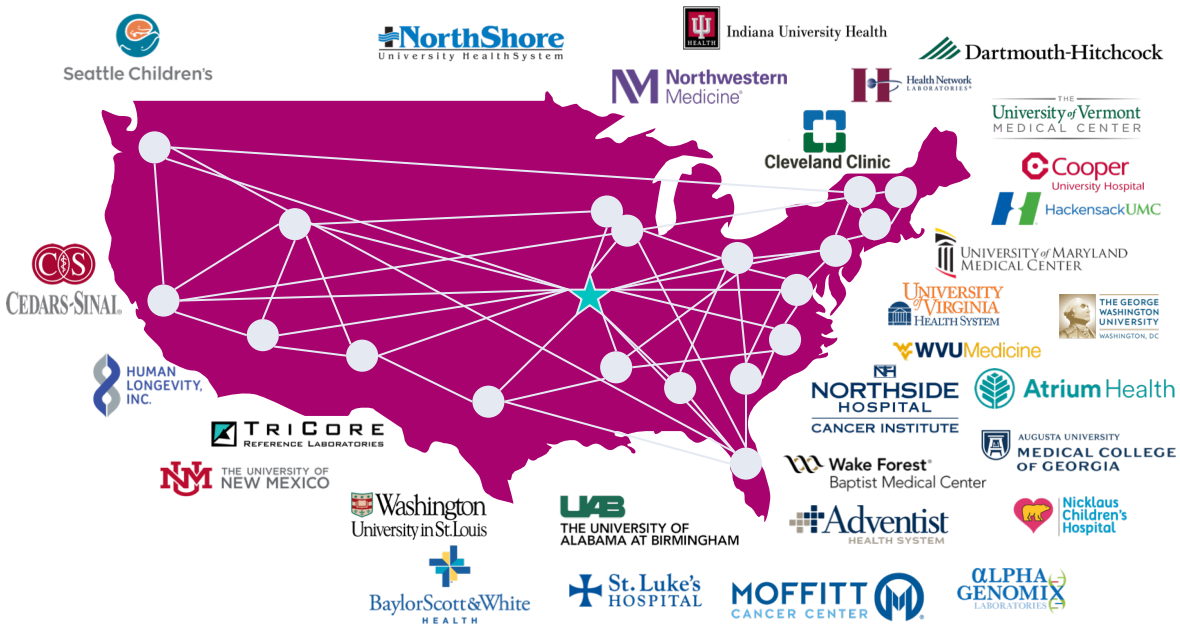
- Scarcity of genomic analysts
- Growing number of assays from multiple vendors
- NGS Test Reimbursement
- Amount of data to curate and interpret from publications
- Rapidly changing therapies, guidelines, clinical trials



BM Good, Genome Biology 2014

PierianDx

Wisdom in Every Report



- **Today:** 45+ health systems and laboratories in partner sharing network
- **2019:** PierianDx signs multi-year deal with Illumina to support cancer research and diagnostics
- **2018:** Moffitt 1st to launch TruSight™ Tumor 170 clinically
- **2014:** PierianDx established; Moffitt Cancer Center 1st to go live
- **2011:** PierianDx technology developed at Washington University in St. Louis

Technology Enabled Services

Clinical Genomics Workspace

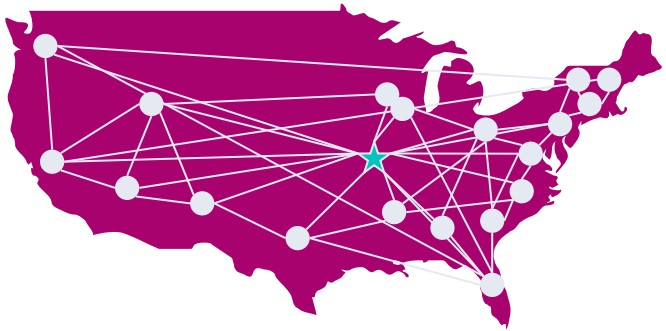
All-in-one informatics and reporting software

Validation & Interpretation Services

Experienced team to fast-track growth

Medically Powered Knowledgebase

The largest opt-in content sharing network



Laboratory Services

Turnkey, validated assays and informatics

Utility and Challenges Associated with Genomic Profiling

Biomarker Detection

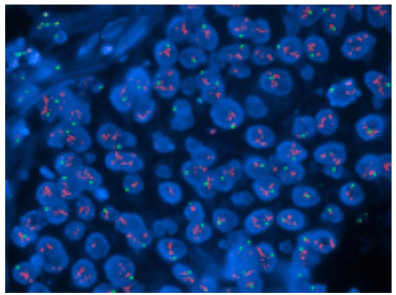
Traditionally for tumor characterization, targets were identified by limited assays

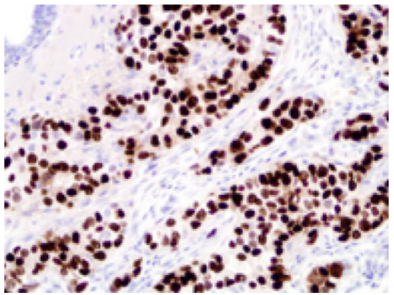
- IHC
- FISH
- Allele specific PCR

Highly specific but provide limited information

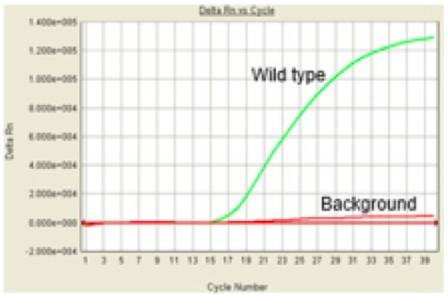
Requires multiple tests for complete analysis

- Increase in markers increases costs and tissue requirements

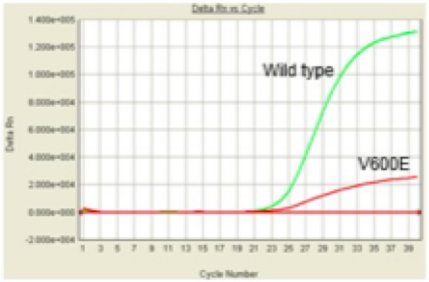




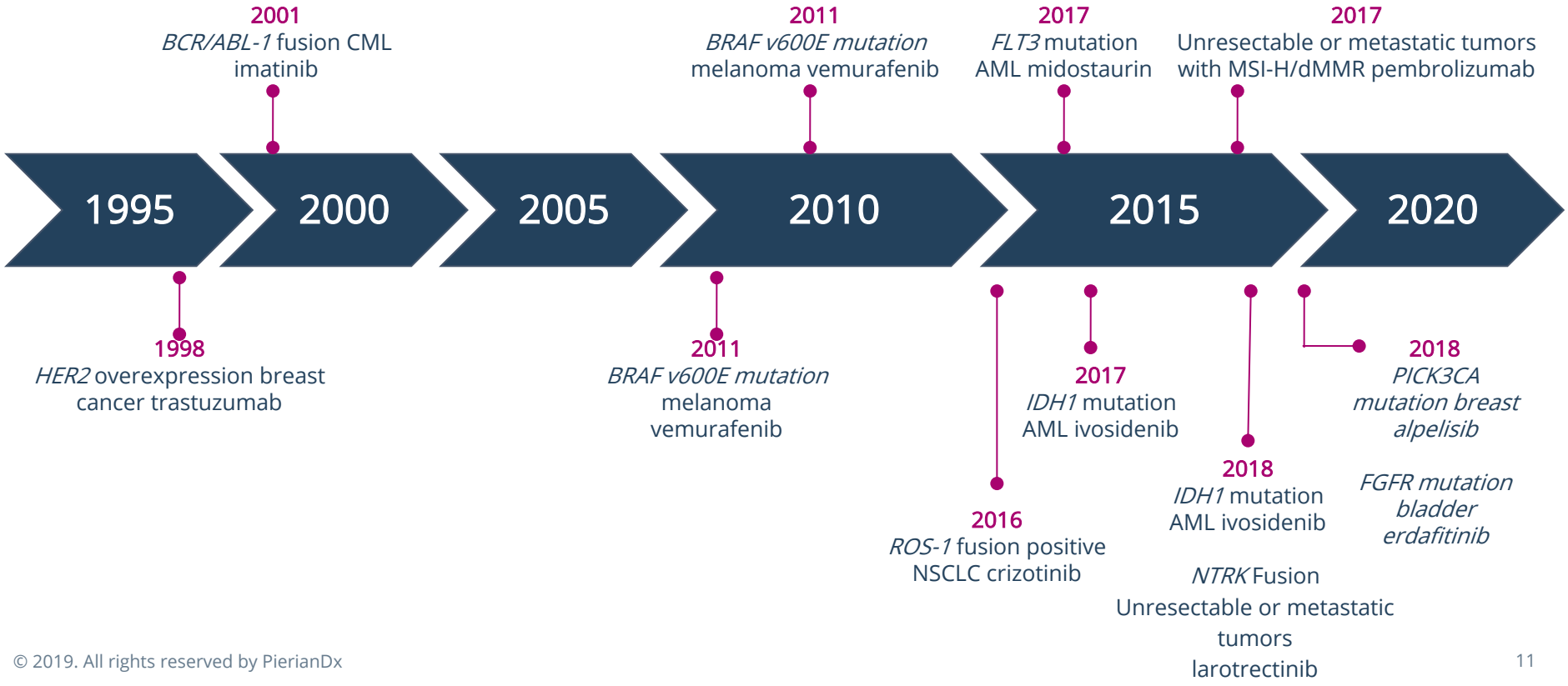
No Mutation Detected



V600E Mutation Detected



Predictive Molecular Biomarkers in Oncology



Next Generation Sequencing

Massively parallel sequencing

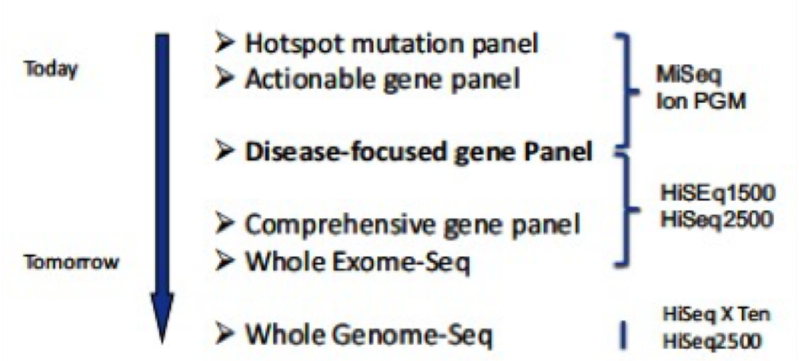
- Allows for large amounts of sequencing relatively cheaply and quickly

Commercially available for over a decade

- Significantly improved in that time
- Currently a very reliable technology

Technical cost now less than analytical

- Depending on panel size can have a very large amount of variants to report



Hotspot Genes (87)			
AKT1	FGFR4	MED12	SRC
AKT2	FLT3	MET	STAT3
AKT3	FOXL2	MTOR	TERT
ALK	GATA2	MYC	TOP1
AR	GNA11	MYCN	U2AF1
ARAF	GNAQ	MYD88	XPO1
AXL	GNAS	NPM1	
BRAF	H3F3A	NRAS	
BTK	HIST1H3B	NTRK1	
CBL	HNF1A	NTRK2	
CCND1	HRAS	NTRK3	
CDK4	IDH1	PDGFRA	
CDK6	IDH2	PDGFRB	
CHEK2	JAK1	PIK3CA	
CSF1R	JAK2	PIK3CB	
CTNNB1	JAK3	PPP2R1A	
DDR2	KDR	PTPN11	
EGFR	KIT	RAC1	
ERBB2	KNSTRN	RAF1	
ERBB3	KRAS	RET	
ERBB4	MAGOH	RHEB	
ERCC2	MAP2K1	RHOA	
ESR1	MAP2K2	ROS1	
EZH2	MAP2K4	SF3B1	
FGFR1	MAPK1	SMAD4	
FGFR2	MAX	SMO	
FGFR3	MDM4	SPOP	

Full-Length Genes (48)	
ARID1A	PALB2
ATM	PIK3R1
ATR	PMS2
ATRX	POLE
BAP1	PTCH1
BRCA1	PTEN
BRCA2	RAD50
CDK12	RAD51
CDKN1B	RAD51B
CDKN2A	RAD51C
CDKN2B	RAD51D
CHEK1	RB1
CREBBP	RNF43
FANCA	SETD2
FANCD2	SLX4
FANCI	SMARCA4
FBXW7	SMARCB1
MLH1	STK11
MRE11A	TP53
MSH2	TSC1
MSH6	TSC2
NBN	
NF1	
NF2	
NOTCH1	
NOTCH2	
NOTCH3	

Copy Number Genes (43)	
AKT1	MDM2
AKT2	MDM4
AKT3	MET
ALK	MYC
AR	MYCL
AXL	MYCN
BRAF	NTRK1
CCND1	NTRK2
CCND2	NTRK3
CCND3	PDGFRA
CCNE1	PDGFRB
CDK2	PIK3CA
CDK4	PIK3CB
CDK6	PPARG
EGFR	RICTOR
ERBB2	TERT
ESR1	
FGF19	
FGF3	
FGFR1	
FGFR2	
FGFR3	
FGFR4	
FLT3	
IGF1R	
KIT	
KRAS	

Gene Fusions (Inter- and intra-genic)	
AKT2	NF1
ALK	NOTCH1
AR	NOTCH4
AXL	NRG1
BRAF	NTRK1
BRCA1	NTRK2
BRCA2	NTRK3
CDKN2A	NUTM1
EGFR	PDGFRA
ERBB2	PDGFRB
ERBB4	PIK3CA
ERG	PPARG
ESR1	PRKACA
ETV1	PRKACB
ETV4	PTEN
ETV5	RAD51B
FGFR1	RAF1
FGFR2	RB1
FGFR3	RELA
FGR	RET
FLT3	ROS1
JAK2	RSPO2
KRAS	RSPO3
MDM4	TERT
MET	
MYB	
MYBL1	

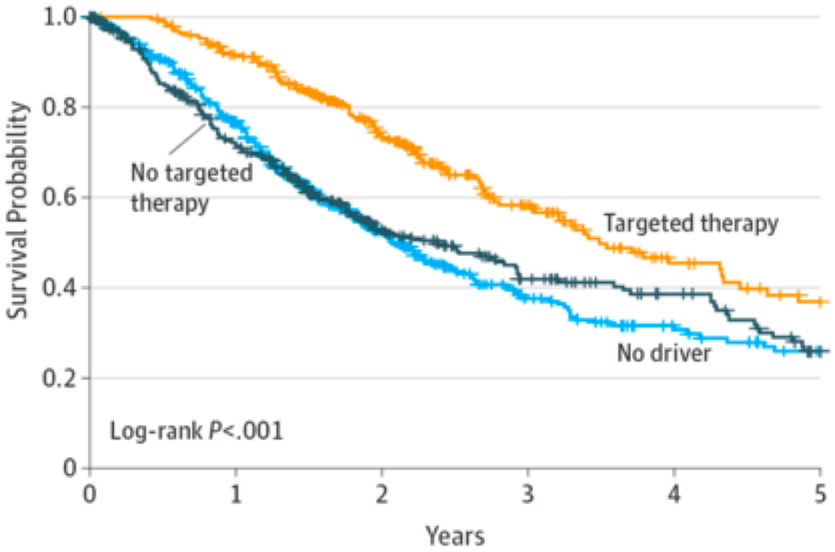
Therapy Selection

15 genes and MSI are FDA approved predictive biomarkers

- *ALK, BRAF, BRCA1/2, EGFR, ERBB2, FGFR2/3, KRAS, NRAS, NTRK1/2/3, PIK3CA, ROS1*
- MSI and *NTRK* pan-tumor, remainder tissue specific

Multiple others have NCCN emerging therapy designation and/or high levels of clinical evidence to support off-label use

- *ATM, MET, PALB2, RET, TMB*



Additional Utility of Genomic Profiling

Clinical Trial Recruitment

- Currently ~5% of patients are added to a clinical trial

Germline variant detection

- Impact for entire families

Diagnostic precision

- Many tumors defined by their molecular event
- Sub-classification of tumors also increasingly driven by genomic profile
- Heme leading but solid tumors will follow

Tissue of origin (primary vs. metastasis)

NCCN National Comprehensive Cancer Network®

"NCCN believes that best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged."

--NCCN Guidelines, 2014

Challenges with Genomic Reporting

Competing audiences

- Different educational backgrounds even within groups
- Different “wants” (sometimes opposing)

Lack of standardization

- Genomic nomenclature can be tricky especially with older “pre-NGS” genes/variants
- Reporting of genomic changes, VAF, CN, fusion transcripts differ lab to lab
- What level of evidence should be used for clinical recommendations?

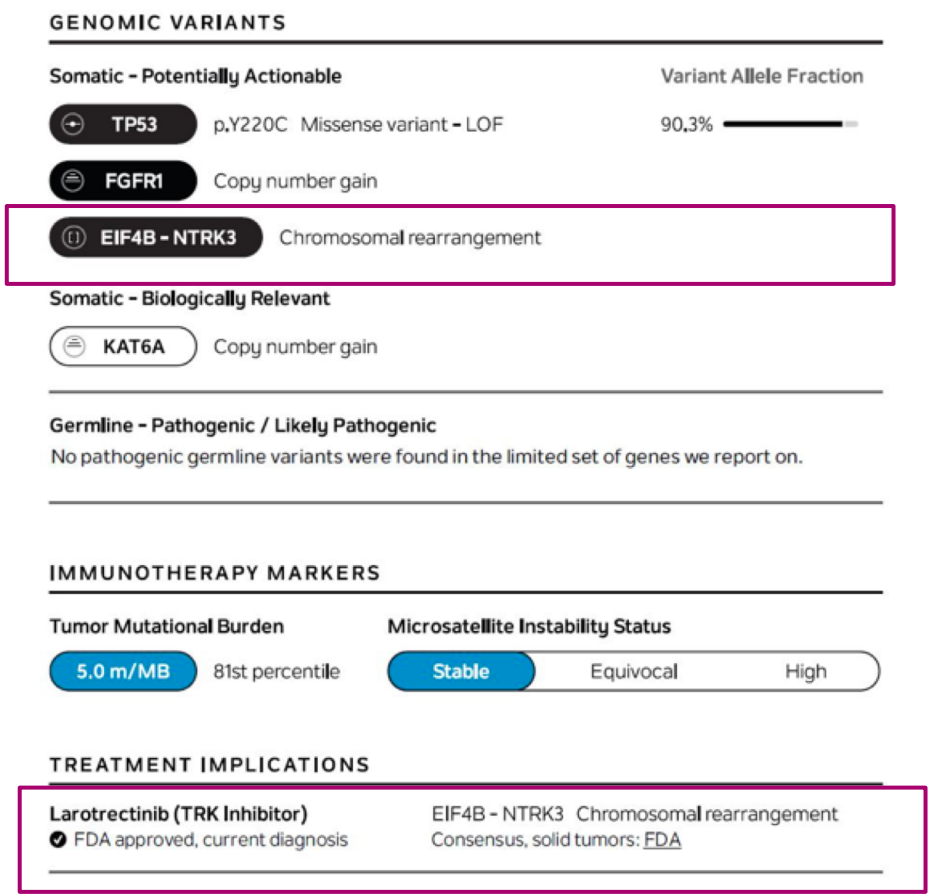
Report findings vs. Analyze findings

- Most labs at least report some analysis of variants
- Matched therapies, clinical trials, guidelines and/or global analysis all can be added on

NTRK Fusion Reporting

NTRK fusions can be reported many different ways

- Note hyphen between fusion partner and gene
- In this example, fusion is referred to as "rearrangement"
- Every laboratory reports *NTRK* fusions slightly differently



NTRK Fusion Reporting

High Impact Results

BIOMARKER	METHOD	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
KRAS	NGS	Mutation Not Detected	BENEFIT	cetuximab, panitumumab	Level 1
NRAS	NGS	Mutation Not Detected			
NTRK1	RNA-Seq	Fusion Detected	BENEFIT	larotrectinib	Level 1
BRAF	NGS	Mutation Not Detected			

* Biomarker reporting classification: Level 1 - highest level of clinical evidence and/or b
and is endorsed by standard clinical guidelines; Level 3 - potential clinical significance

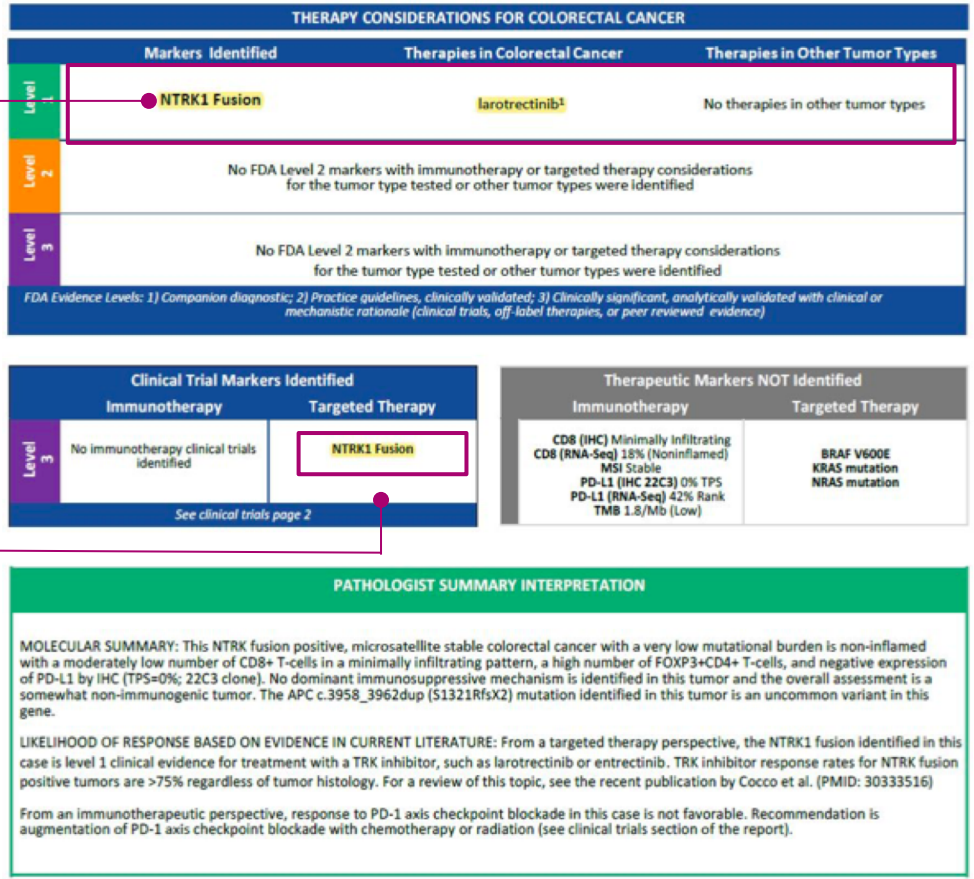
- Larotrectinib is included in the therapy association
- Prominent use of the word “fusion”
- Note hyphen between fusion partner and gene

Important Note

A TPM3-NTRK1 gene fusion was detected in this tumor. This fusion has been previously reported in several different tumors (Ardini 2014 Mol Oncol 8:1495; Chiang 2018 Am J Surg Pathol 42:791).

NTRK Fusion Reporting

- Does not include the fusion partner
- Larotrectinib is listed as therapy
- Prominent use of the word “fusion”



THERAPY CONSIDERATIONS FOR COLORECTAL CANCER

	Markers Identified	Therapies in Colorectal Cancer	Therapies in Other Tumor Types
Level 1	NTRK1 Fusion	larotrectinib[1]	No therapies in other tumor types
Level 2	No FDA Level 2 markers with immunotherapy or targeted therapy considerations for the tumor type tested or other tumor types were identified		
Level 3	No FDA Level 2 markers with immunotherapy or targeted therapy considerations for the tumor type tested or other tumor types were identified		

FDA Evidence Levels: 1) Companion diagnostic; 2) Practice guidelines, clinically validated; 3) Clinically significant, analytically validated with clinical or mechanistic rationale (clinical trials, off-label therapies, or peer reviewed evidence)

Clinical Trial Markers Identified		
	Immunotherapy	Targeted Therapy
Level 3	No immunotherapy clinical trials identified	NTRK1 Fusion

See clinical trials page 2

Therapeutic Markers NOT Identified	
Immunotherapy	Targeted Therapy
CD8 (IHC) Minimally Infiltrating **CD8 (RNA-Seq)** 18% (Noninflamed) **MSI** Stable **PD-L1 (IHC 22C3)** 0% TPS **PD-L1 (RNA-Seq)** 42% Rank **TMB** 1.8/Mb (Low)	**BRAF V600E** **KRAS mutation** **NRAS mutation**

PATHOLOGIST SUMMARY INTERPRETATION

MOLECULAR SUMMARY: This NTRK fusion positive, microsatellite stable colorectal cancer with a very low mutational burden is non-inflamed with a moderately low number of CD8+ T-cells in a minimally infiltrating pattern, a high number of FOXP3+CD4+ T-cells, and negative expression of PD-L1 by IHC (TPS=0%; 22C3 clone). No dominant immunosuppressive mechanism is identified in this tumor and the overall assessment is a somewhat non-immunogenic tumor. The APC c.3958_3962dup (S1321RfsX2) mutation identified in this tumor is an uncommon variant in this gene.

LIKELIHOOD OF RESPONSE BASED ON EVIDENCE IN CURRENT LITERATURE: From a targeted therapy perspective, the NTRK1 fusion identified in this case is level 1 clinical evidence for treatment with a TRK inhibitor, such as larotrectinib or entrectinib. TRK inhibitor response rates for NTRK fusion positive tumors are >75% regardless of tumor histology. For a review of this topic, see the recent publication by Cocco et al. (PMID: 30333516)

From an immunotherapeutic perspective, response to PD-1 axis checkpoint blockade in this case is not favorable. Recommendation is augmentation of PD-1 axis checkpoint blockade with chemotherapy or radiation (see clinical trials section of the report).

NTRK Fusion Reporting

- Note hyphen between fusion partner and gene
- Larotrectinib is not listed as therapy on this page
- Prominent use of the word “fusion”

Companion Diagnostic (CDx) Associated Findings

GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
KRAS wildtype (codons 12 & 13)	Erbitux® (Cetuximab)
KRAS/NRAS wildtype (codons 12, 13, 59, 61, 117, & 146 in exons 2, 3, & 4)	Vectibix® (Panitumumab)

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for additional information.

Microsatellite status MSI-High §
Tumor Mutational Burden 34 Muts/Mb §
ASXL1 G645fs*58
CIC G136fs*8
CREBBP H2384fs*12
FLCN H429fs*39

NTRK1 TPM3(NM_152263)-NTRK1(NM_002529) fusion (T10*; N10) §
RNF43 R286W
RNF43 G659fs*41
SOX9 Q357*
TSC2 G654fs*2

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, MSI or TMB result in this section.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

NTRK Fusion Reporting

- Note hyphen between fusion partner and gene
- Larotrectinib is listed as therapy with clinical benefit
- Prominent use of the word “fusion”

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Microsatellite status - MSI-High	Nivolumab	none
	Pembrolizumab	
10 Trials *see p. 15*		
Tumor Mutational Burden - TMB-High (34 Muts/Mb)	none	Atezolizumab
		Avelumab
		Durvalumab
		Nivolumab
		Pembrolizumab
10 Trials *see p. 17*		
GENOMIC FINDINGS	**THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)**	**THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)**
NTRK1 - TPM3-NTRK1 fusion	Larotrectinib	Crizotinib
8 Trials *see p. 19*		
RNF43 - G659fs*41, R286W	none	none
2 Trials *see p. 21*		
TSC2 - G654fs*2	none	none
10 Trials *see p. 22*		

NTRK Fusion Reporting

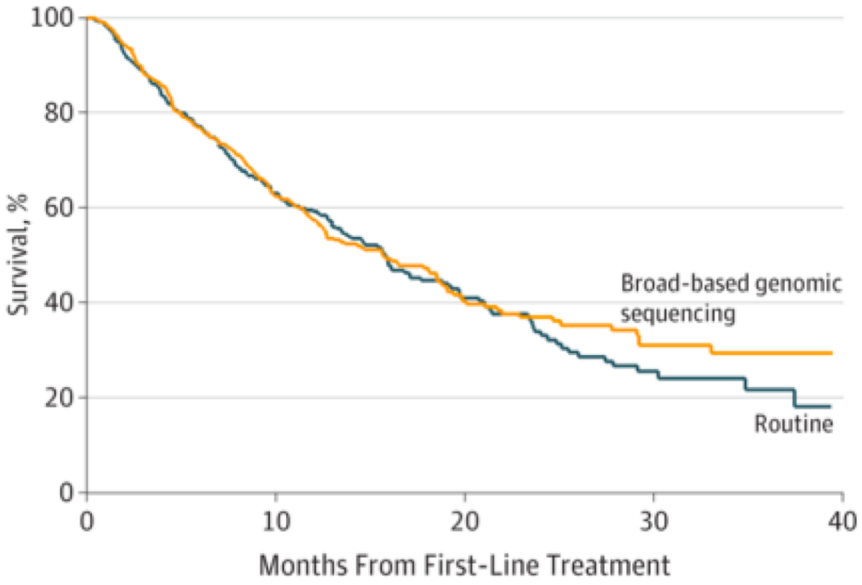
***NTRK1* Point Mutation vs. Fusion**

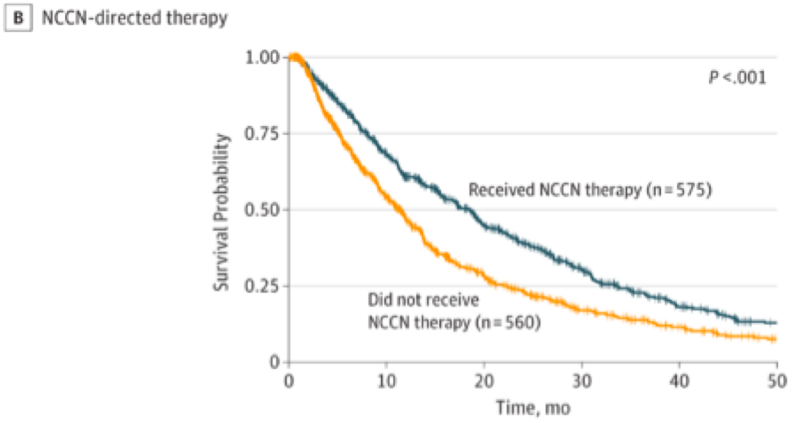
- Do not confuse NTRK1 point mutation with "fusion."
- Point mutation is not part of the indication for larotrectinib.
- Anecdotal findings suggest that larotrectinib does not work in these patients.

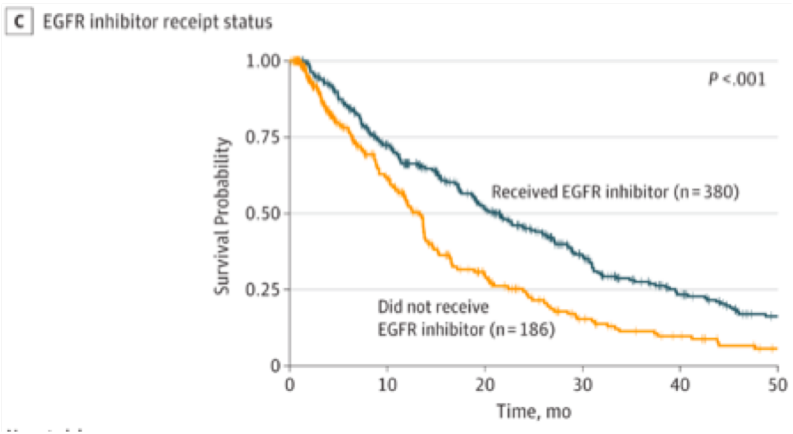
Variants of Unknown Significance

Gene	Variant
NOTCH3	P.R544C chr19:g.15298126G>A NM_000435 2:c.1630C>T
NTRK1	p.Q80R chr1:g.156834172A>G NM_002529. 3:c.239A>G
TSC2	p.P330L chr16:g.2110684C>T NM_000548.3:c.989C>T
ARID1A	p.G1254S chr1:g.27099881G>A NM_006015.4:c.3760G>A

Why is this Important?







How can Pathology Help?

1

Comprehensive analysis and reporting

- Utilize EMR in crafting reports for true personalization
- Provide updates on novel therapeutics
- Hand match clinical trials in and outside network
- Explain discordant results

2

Outreach and education

- Both clinicians and general pathologists
- Builds personal relationships and trust in the laboratory
- Generally enhances patient care

Structure of Cedars-Sinai Reports

First page has everything really important for patient care

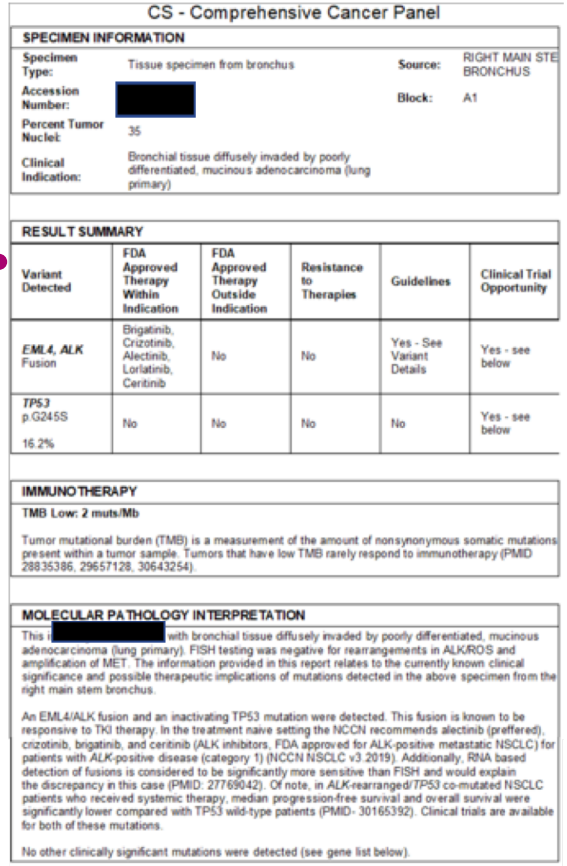
Summary of results with therapies and guidelines

Molecular pathology interpretation

- Provides personalized, in-depth analysis
- Lists relevant therapies and guidelines
- Suggests relevant clinical trials

Remaining (3-5) pages has everything else

- Clinical trial details
- Variant details
- VUS
- Regulatory requirements (disclaimers, methodology etc.)



CS - Comprehensive Cancer Panel

SPECIMEN INFORMATION

Specimen Type:	Tissue specimen from bronchus	**Source:**	RIGHT MAIN STE BRONCHUS
Accession Number:	[redacted]	**Block:**	A1
Percent Tumor Nuclei:	35		
Clinical Indication:	Bronchial tissue diffusely invaded by poorly differentiated, mucinous adenocarcinoma (lung primary)		

RESULT SUMMARY

Variant Detected	FDA Approved Therapy Within Indication	FDA Approved Therapy Outside Indication	Resistance to Therapies	Guidelines	Clinical Trial Opportunity
EML4, ALK Fusion	Brigatinib, Crizotinib, Alectinib, Lorlatinib, Ceritinib	No	No	Yes - See Variant Details	Yes - see below
TP53 p.G245S 16.2%	No	No	No	No	Yes - see below

IMMUNOTHERAPY

TMB Low: 2 muts/Mb

Tumor mutational burden (TMB) is a measurement of the amount of nonsynonymous somatic mutations present within a tumor sample. Tumors that have low TMB rarely respond to immunotherapy (PMID 28835386, 29657128, 30643254).

MOLECULAR PATHOLOGY INTERPRETATION

This [redacted] with bronchial tissue diffusely invaded by poorly differentiated, mucinous adenocarcinoma (lung primary). FISH testing was negative for rearrangements in ALK/ROS and amplification of MET. The information provided in this report relates to the currently known clinical significance and possible therapeutic implications of mutations detected in the above specimen from the right main stem bronchus.

An EML4/ALK fusion and an inactivating TP53 mutation were detected. This fusion is known to be responsive to TKI therapy. In the treatment naive setting the NCCN recommends alectinib (preffered), crizotinib, brigatinib, and ceritinib (ALK inhibitors, FDA approved for ALK-positive metastatic NSCLC) for patients with *ALK*-positive disease (category 1) (NCCN NSCLC v3.2019). Additionally, RNA based detection of fusions is considered to be significantly more sensitive than FISH and would explain the discrepancy in this case (PMID: 27769042). Of note, in *ALK*-rearranged/*TP53* co-mutated NSCLC patients who received systemic therapy, median progression-free survival and overall survival were significantly lower compared with TP53 wild-type patients (PMID- 30165392). Clinical trials are available for both of these mutations.

No other clinically significant mutations were detected (see gene list below).

Explanation of Rare Variants

Sequencing produces many rare variants

- Clinicians are often unprepared to evaluate them
- Need for descriptive reporting and direct consultation
- Often have molecular studies that seem discrepant
- EMR is crucial in these cases

Results Summary

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

49 y/o m with metastatic (bone & brain) NSCLC

- *EGFR* (Sanger), *BRAF* (PCR) and *PD-L1* (IHC) negative at OSH
- Remaining biomarkers QNS

Came to Cedars-Sinai for treatment

- Repeated biopsy to complete molecular profile

Found to have an EGFR KDD (exon 18-25)

- Rare activating *EGFR* variant (~1% of EGFR mut)
- Sparse clinical evidence suggests sensitivity to TKI therapy (particularly afatinib)

Discussed findings with clinician prior to and during tumor board

- Explained discrepancy with prior *EGFR* study
- Osimertinib ultimately chosen (Brain penetration)

Patient started therapy and has had complete symptom relief and radiographic shrinkage of the brain and bone mets

Updating Targeted Therapies

Molecular therapeutics is advancing rapidly

- Novel therapies are continually being approved
- Often therapies that work on a target in one tumor type work in another
- No patient should miss out if available

Variant Detected	FDA Approved Therapy Within Indication	FDA Approved Therapy Outside Indication	Resistance to Therapies	Guidelines	Clinical Trial Opportunity
FGFR3, TACC3 Fusion	No	No	No	No	Yes - see below
TP53 p.G245C 49.4%	No	No	No	No	Yes - see below
CDK4 Amplification	No	No	No	No	Yes - see below
FGFR3 Amplification	No	No	No	No	Yes - see below
CCND2 Amplification	No	No	No	No	Yes - see below

73 y/o female with GBM diagnosed August of last year

Found to have an FGFR3-TACC3 fusion

- At the time no targeted therapies, just trials

Received standard of care (TMZ, radiation)

- Developed aplastic anemia and was no longer eligible for clinical trial
- Considering hospice

Erdafitinib (FGFR TKI) approved recently for FGFR2/3 mutated urothelial carcinoma

- Queried database for patients with those mutations (pan-cancer)
- Reached out to clinician and amended report to include this as off label therapy
- Patient was able to recently obtain and begin treatment

Clinical Trial Matching

Most patients have a variant with an open related clinical trial

Including clinical trials on the report is an area of disagreement between clinicians

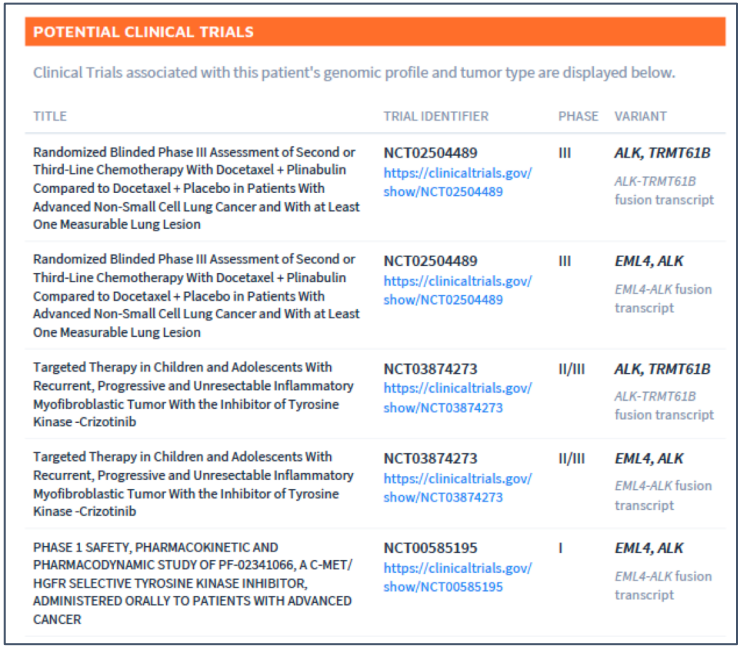
- Some utilize it, some skip right over
- How can we make higher yield?

Curating them takes a lot of work

- Easily searchable/automatable databases help
- Still large manual portion

Will include trials in the first page interpretation when especially clinically relevant

- In system or local area a big plus
- Good published clinical data
- Example: EGFR/ERBB2 exon 20 insertions referred to trial treating with poziotinib at an outside institution.



POTENTIAL CLINICAL TRIALS

Clinical Trials associated with this patient's genomic profile and tumor type are displayed below.

TITLE	TRIAL IDENTIFIER	PHASE	VARIANT
Randomized Blinded Phase III Assessment of Second or Third-Line Chemotherapy With Docetaxel + Plinabulin Compared to Docetaxel + Placebo in Patients With Advanced Non-Small Cell Lung Cancer and With at Least One Measurable Lung Lesion	NCT02504489 https://clinicaltrials.gov/show/NCT02504489	III	***ALK, TRMT61B*** *ALK-TRMT61B* fusion transcript
Randomized Blinded Phase III Assessment of Second or Third-Line Chemotherapy With Docetaxel + Plinabulin Compared to Docetaxel + Placebo in Patients With Advanced Non-Small Cell Lung Cancer and With at Least One Measurable Lung Lesion	NCT02504489 https://clinicaltrials.gov/show/NCT02504489	III	***EML4, ALK*** *EML4-ALK* fusion transcript
Targeted Therapy in Children and Adolescents With Recurrent, Progressive and Unresectable Inflammatory Myofibroblastic Tumor With the Inhibitor of Tyrosine Kinase -Crizotinib	NCT03874273 https://clinicaltrials.gov/show/NCT03874273	II/III	***ALK, TRMT61B*** *ALK-TRMT61B* fusion transcript
Targeted Therapy in Children and Adolescents With Recurrent, Progressive and Unresectable Inflammatory Myofibroblastic Tumor With the Inhibitor of Tyrosine Kinase -Crizotinib	NCT03874273 https://clinicaltrials.gov/show/NCT03874273	II/III	***EML4, ALK*** *EML4-ALK* fusion transcript
PHASE 1 SAFETY, PHARMACOKINETIC AND PHARMACODYNAMIC STUDY OF PF-02341066, A C-MET/HGFR SELECTIVE TYROSINE KINASE INHIBITOR, ADMINISTERED ORALLY TO PATIENTS WITH ADVANCED CANCER	NCT00585195 https://clinicaltrials.gov/show/NCT00585195	I	***EML4, ALK*** *EML4-ALK* fusion transcript

Tumor Mutation Burden (TMB)

Gold standard is T/N exome

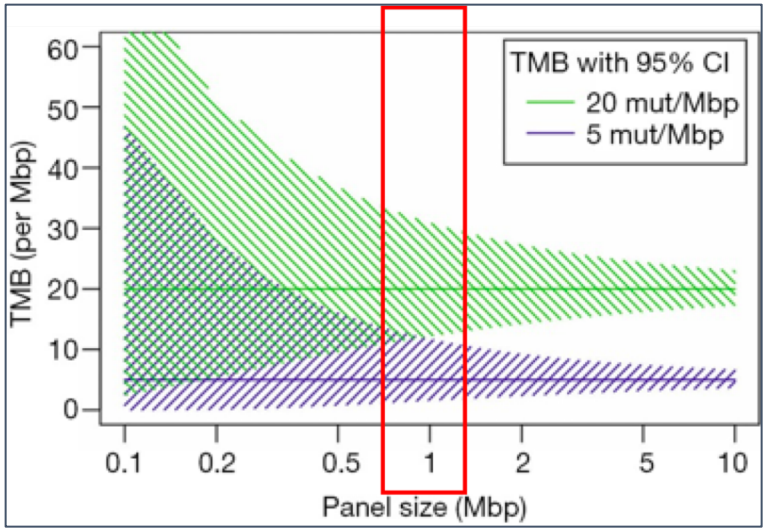
- Mostly done clinically with tumor only panels

Currently reported as a category and a number

- High – ≥10 mutations/Mb
- Intermediate – 5-9 mutations/Mb
- Low - ≤4 mutations/Mb

"One size fits all approach"

Does this really translate from tumor to tumor?



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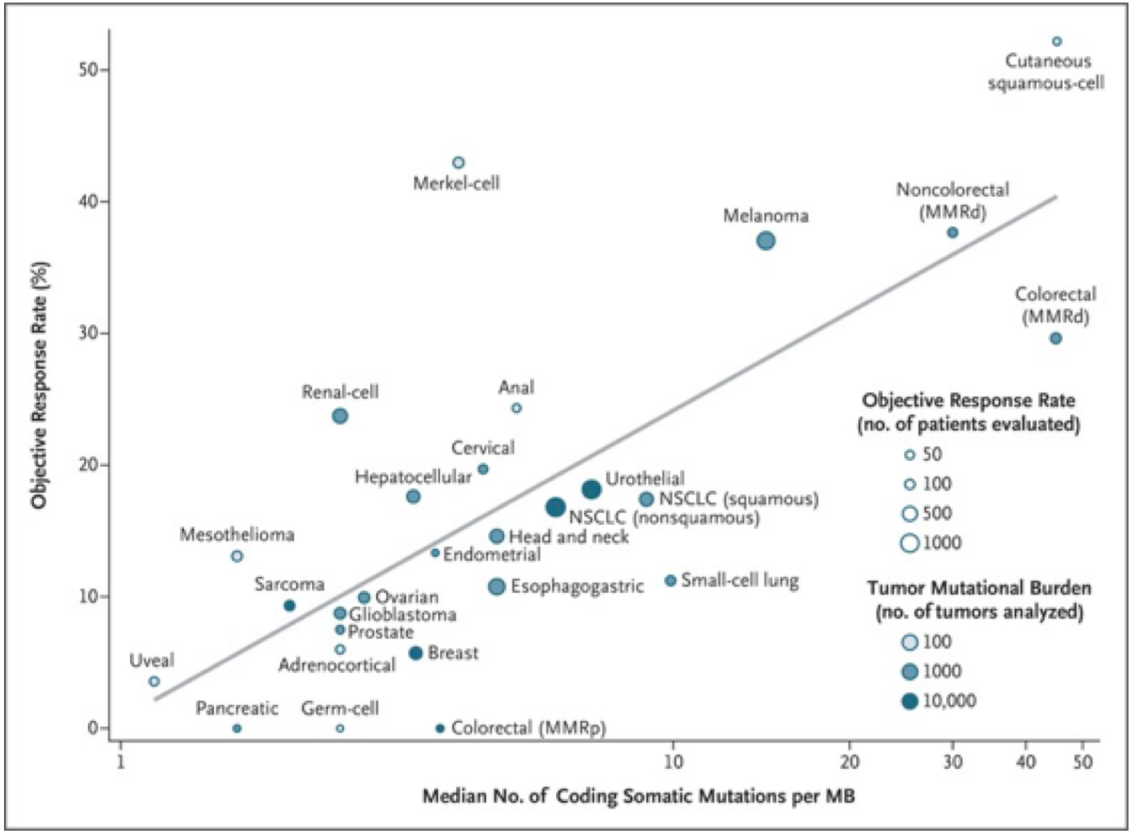
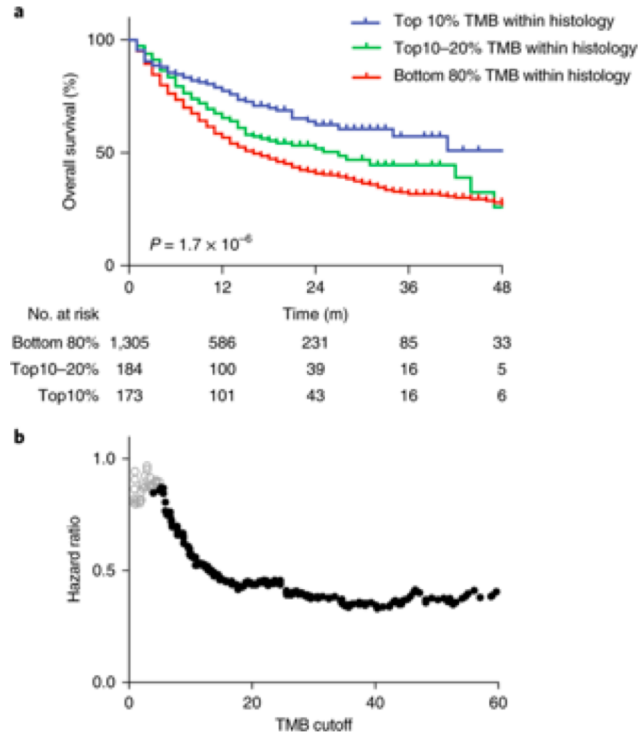
TMB Reporting





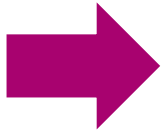
Visibility of Reporting

Reports are often PDFs

- Not discrete (unsearchable)
- Disconnected from the histopathology
- Easily lost in the shuffle of the dreaded media tab

May lead to situations where molecular results are never reviewed!

Multiple possible solutions



Direct discrete data integration into EMR

Molecular consult notes

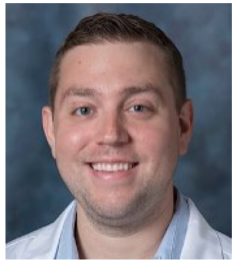
EMR alerts

Summary

- Genomic profiling provides **high value for patients and laboratories**
- Molecular oncology reporting is **highly complex**
- Differences in reporting have real-world clinical impact. **Standardization and integration with EMR can help mitigate challenges**.
- When in doubt, **pick up the phone!**

Questions and Answers

Eric Vail, MD
Director, Molecular Pathology
Cedars-Sinai Medical Center



Rakesh Nagarajan, MD, PhD
Executive Chairman and Founder
PierianDx