

Real world delivery of cancer precision medicine: The UCSF experience

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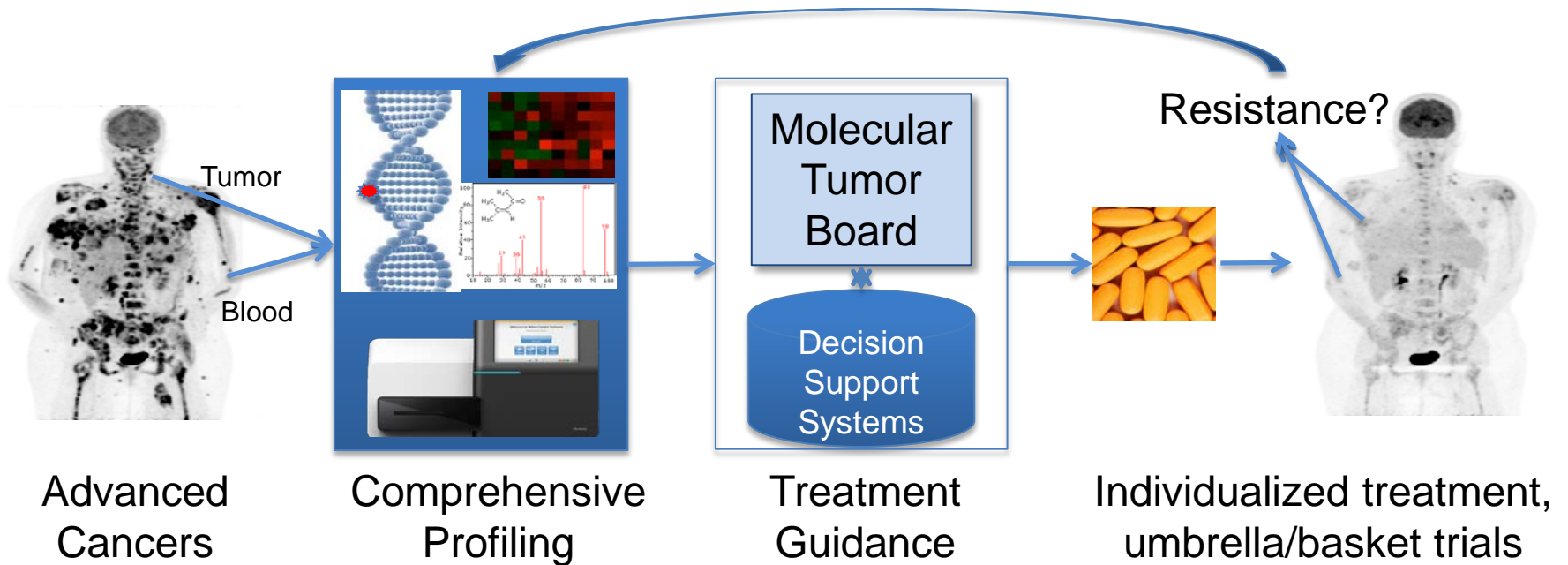
Benioff UCSF Professor of Children's Health
Head, UCSF Molecular Oncology Initiative

PMWC 2019

Mountain View, CA

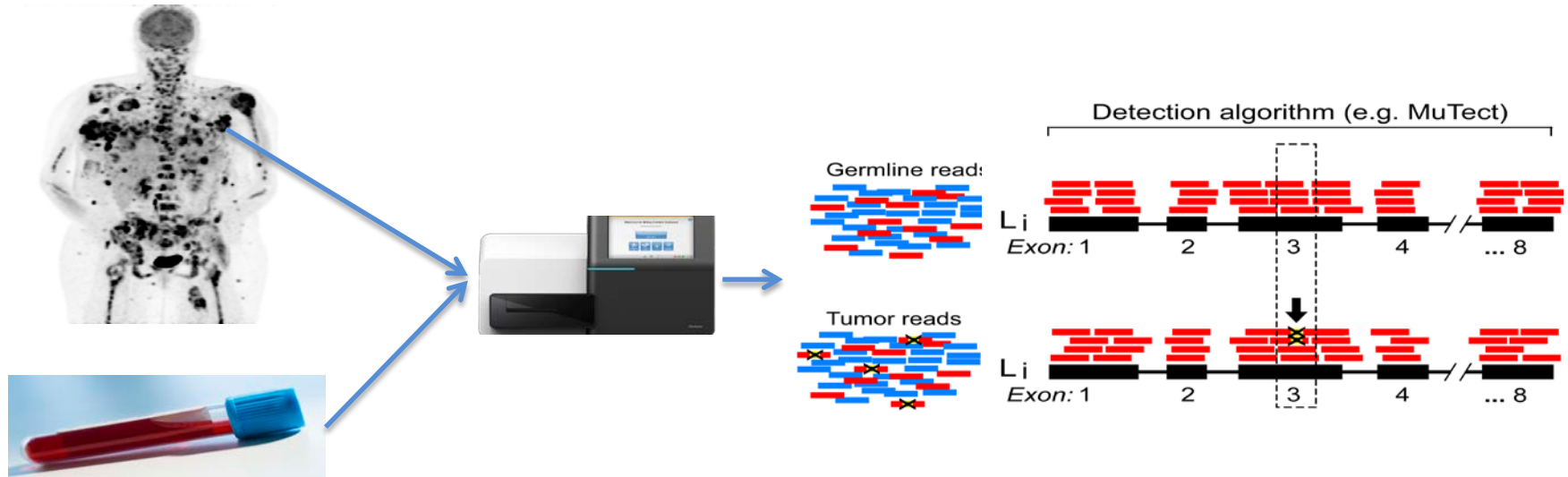


Precision Cancer Medicine



Better Predictions • Improved Outcomes • Less Toxicity

UCSF500: Paired normal/tumor DNA next-generation sequencing assay



- CLIA-approved – available to patients seen across UCSF sites

UCSF500 Technical specifications

- UCSF pediatric AND adult oncology community consulted for inclusion of genes relevant to their diseases of interest
- Tumor DNA extracted from FFPE + normal DNA
- Exon tiling across 479 genes
- Selected intron tiling across 47 genes.
- Selected probes across genome to report copy number
- Average read depth 500X
- Variant pipeline in DNAnexus
- Report generated using Genome Oncology platform

UCSF500 Panel Assay

- Current volume ~100 sequenced cases/month
- First case signed-out April of 2015
- >2000 cases reported to date
- 80% Adult, 20% Pediatric
- Data imported and visualized using a local cbiportal instance
- Manuscript reporting results on initial 2000+ cases in preparation

UCSF Molecular Tumor Board



- Held every two weeks
- Cases discussed by physician request (4-8 cases/session)
- Both UCSF and outside referrals (Kaiser, UC Davis, Valley Children's Hospital, many others)
- Cases discussed prepared/discussed by referring clinician, molecular pathologist and oncologist with molecular expertise (Moasser, Collisson, Stieglitz, Klein, Sweet-Cordero)
- Sessions attended by core group of pediatric/adult clinicians with wide disease-specific expertise as well as geneticists, pharmacists and others.
- Written report provided to clinicians
- IRB approved Registry Trial

UCSF500 Report

Access Only

Gene	Transcript ID	Classification	Phase	Mutant Allele Frequency
BRCA1	BRCA1-AS1	Gene Deletion	IVB	0%
BRCA1	BRCA1	Gene Deletion	IVB	0%
BRCA2	BRCA2-AS1	Gene Deletion	IVB	0%
BRCA2	BRCA2	Gene Deletion	IVB	0%
TP53	TP53	Point Mutation	IVB	100%
PTEN	PTEN	Gene Deletion	IVB	0%
SMAD4	SMAD4	Gene Deletion	IVB	0%
SMAD4	SMAD4-AS1	Gene Deletion	IVB	0%

Gene	Transcript ID	Classification	Phase	Mutant Allele Frequency
TP53	TP53	Point Mutation	IVB	100%

INTERPRETATION
Publicly facing to the testing only.

Gene	Transcript ID	Classification	Phase	Mutant Allele Frequency
TP53	TP53	Point Mutation	IVB	100%

Molecular Tumor Board

Utility of Test

Change in Diagnosis

Biomarker-guided treatment options

Risk Stratification

Cancer Genetics (germline findings)

- Biweekly meetings
- A team molecular pathologists, genetic counselors and clinicians with genomics expertise research variants/genes in report
- Clinical hx of patient, UCSF500 results, and recommendations discussed at meeting
- Recommendation report provided

CLINICAL OUTCOME TRACKING

UCSF Molecular Tumor Board Recommendation

Ordering MD: Colson
 Date of Discussion: 12.17.2018
 Patient Name: Jane Doe
 DOB: MM/DD/YYYY
 MRN: xxx
 M/TB Case Number: M/TB-1187
 Report Number: CCG-xxxx
 Diagnosis: Liver Cholangiocarcinoma

Final Recommendation:

- Binimetinib (MEK inhibitor) in combination with cetuximab (EGFR inhibitor)

Summary of Molecular Tumor Board Recommendations

Clinically Actionable Variants	Recommended Action	Comment
BRCA1/2/3	RTX inhibitor + MEK inhibitor (no co-existing genetic mutations in tumor that would result in constitutive Ras activation)	This is a "class 3" BRAF mutant! Class 3 mutants are sensitive to ERK-mediated feedback and their activation of signaling is Ras-dependent (in contrast to the classic "class 1" V600E mutants). As they are dependent on

The UCSF500 Report

Patient: A.C. CCGL No: CCGL-733 1

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Executive Director: Boris C. Bastian, MD
Medical Director: James P. Grenert, MD, PhD
Associate Directors: Jessica Van Ziffle, PhD
Iwei Yeh, MD, PhD

UCSF 500 Cancer Panel Final Report CCGL No: CCGL-733
Date: 01/26/2017

Patient: [Redacted] MRN: {Redacted}	DOB: [Redacted] Sex: Male	Tumor <i>Source:</i> C16-22808 A1; Liver, Solid Tissue (CGP-3652) <i>Diagnosis:</i> Adenocarcinoma <i>Collected:</i> 12/27/2016
Ordering Provider(s): Jonathan Chou, MD Cytopathologist: Theodore Miller, MD Electronically Signed-Out by: Boris Bastian, MD		Normal <i>Source:</i> , Blood (CGP-3651) <i>Collected:</i> 12/29/2016

Pathogenic or Likely Pathogenic S
VARIANT
APC p.C110fs
BRCA2 p.V2908fs
CDKN2A p.M52K
PBRM1 p.S295*
FAT3 c.10559_10566+15del
STAG2 c.1535-1G>C
MYB amplification
<small>'Reads' indicate the number of unique DNA molecules and is affected by the degree of normal cell content</small>
Pathogenic or Likely Pathogenic G
VARIANT
BRCA2 c.1054dupT, p.Y352fs

Clinical Utility of UCSF500 Testing

Uncover cancer risk traits

Detection of therapeutic targets

Firmly establish diagnosis

→

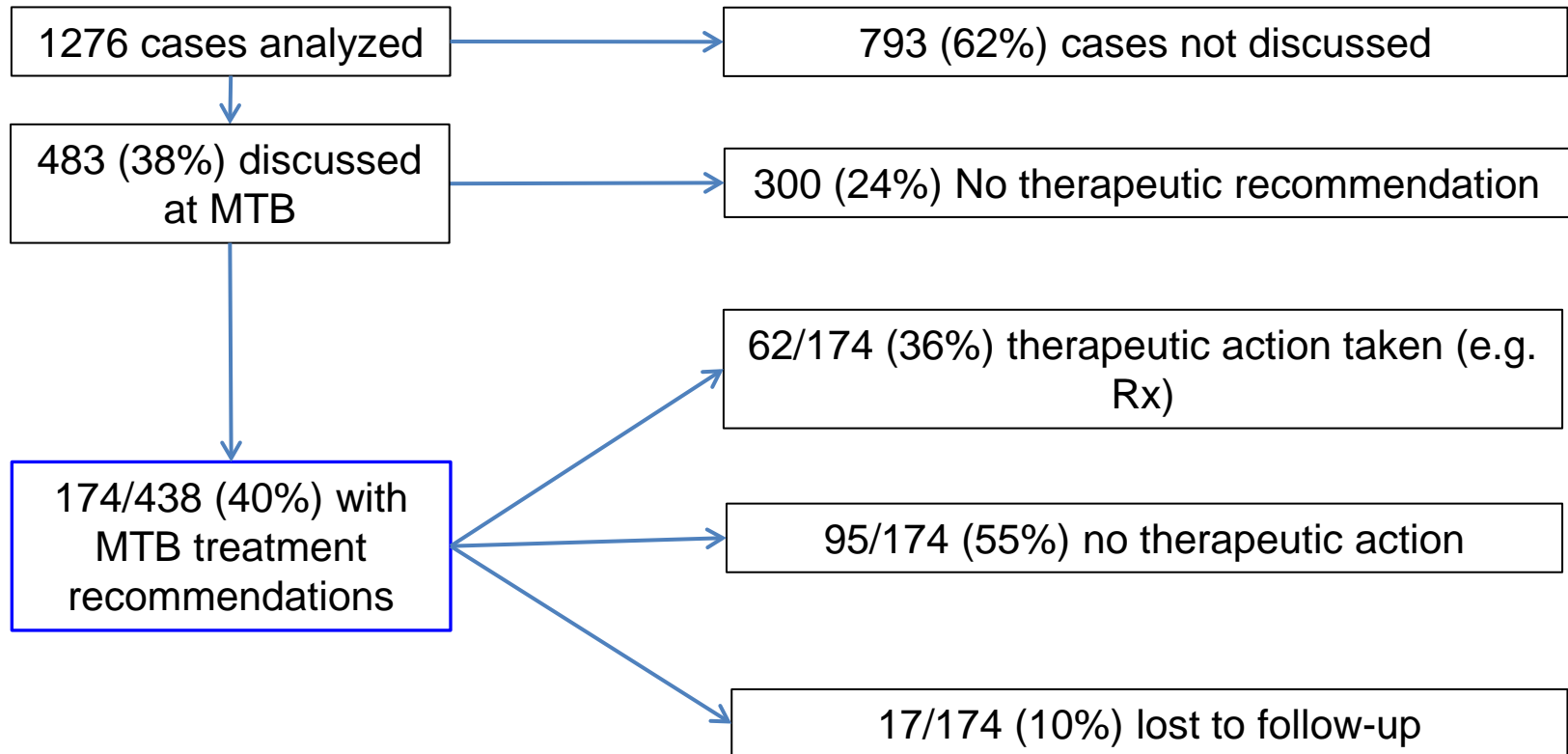
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UCSF500 – Molecular Tumor Board - Patient Flow



Updated to April, 2018

Case Study #1: Change in Diagnosis leading to appropriate targeted therapy

MTB Case Study: Change in Diagnosis

1/15: 20 year old man presented with left-sided hip pain and intermittent fevers. **Clinical Diagnosis: Ewing sarcoma.**

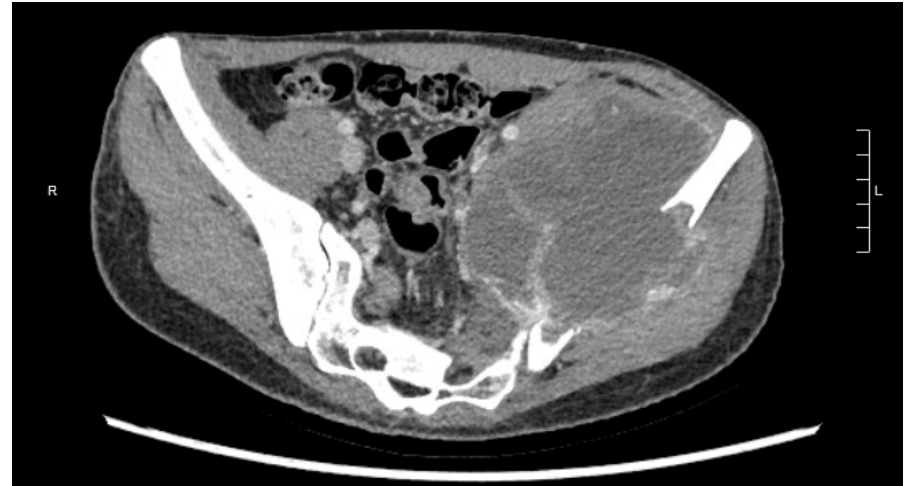
3/15: chemotherapy initiated.

5/15: no response to treatment, ongoing daily fevers, weight loss 50 lbs, bed ridden.

6/15: UCSF500: EWSR1-ATF1 fusion, indicative of **histiocytoma**, not Ewing sarcoma.

6/15: Specific treatment (anti-IL-6) initiated. Fevers resolved.

12/15: Tumor resected



7% of all UCSF500 analyses result in changes of the diagnosis

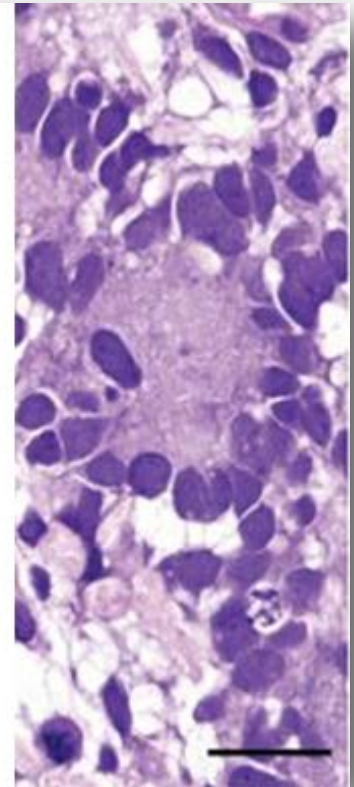
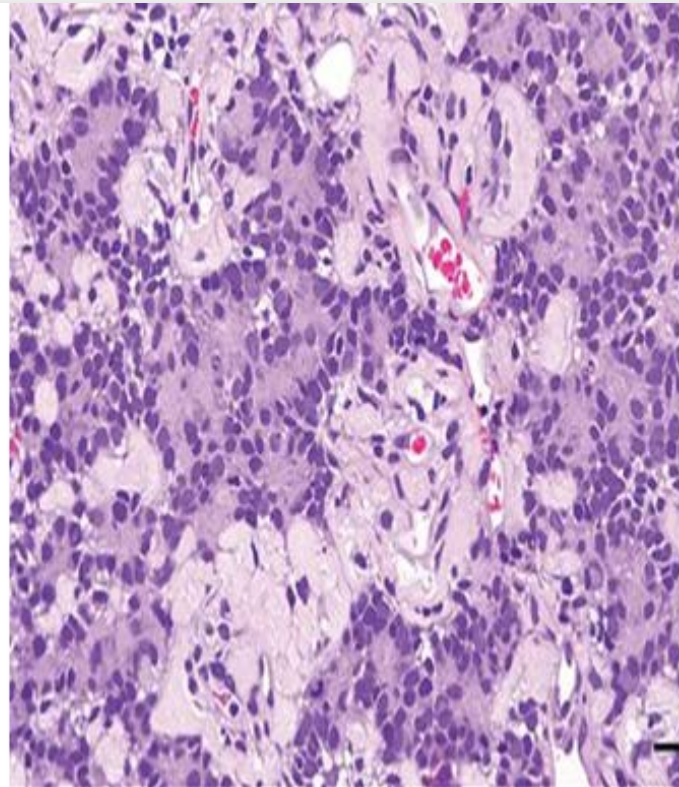
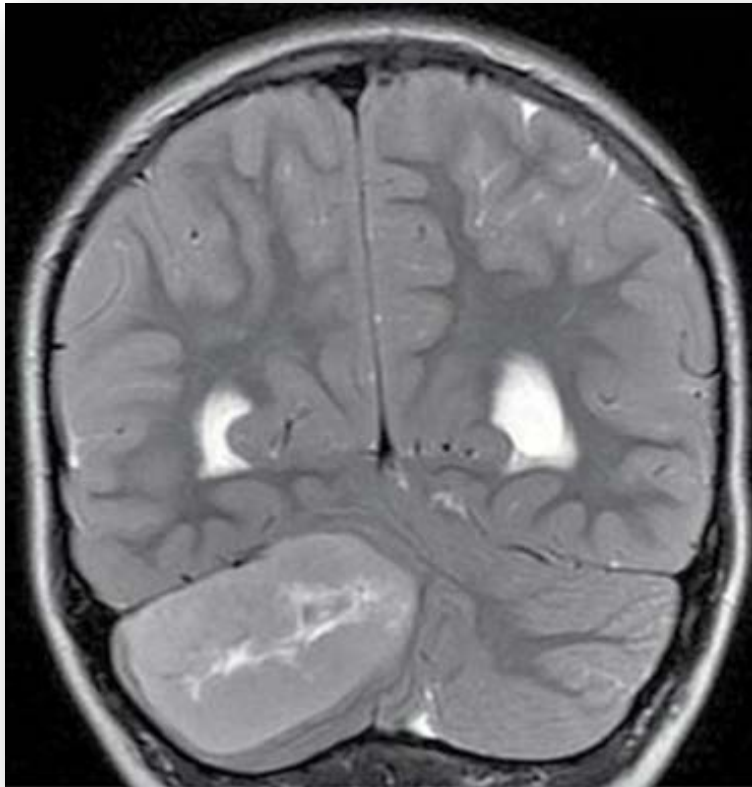
Case Study #2: CNS tumors change in diagnosis leading to management change

Case Study #2: CNS tumors change in diagnosis leading to management change

- 4-year-old girl diagnosed as anaplastic medulloblastoma by referring provider
- Synaptophysin/neurofilament neg. and patchy OLIG2 staining not seen in medulloblastoma
- Internal tandem duplication within exon 15 of BCOR
- Amended diagnosis of CNS high-grade neuroepithelial tumor with BCOR alteration
- Because newly described, challenging to ascertain prognosis or identify best therapy; however, indicative of importance of correct identification → previously would have been inaccurately identified as MB and therefore would never have known to look for reasons why didn't respond or why outcome different without knowing actual diagnosis was wrong → ***how do we know what we don't know?***

MTB Case Study: Change in diagnosis

Medulloblastoma to CNS high-grade neuroepithelial tumor with *BCOR* alteration



Courtesy of Dr. Cassie Kline

Highly cellular tumor with rosettes, scattered pseudorosettes, and areas of necrosis

MTB Case Study: Change in diagnosis



Courtesy of Dr. Cassie Kline

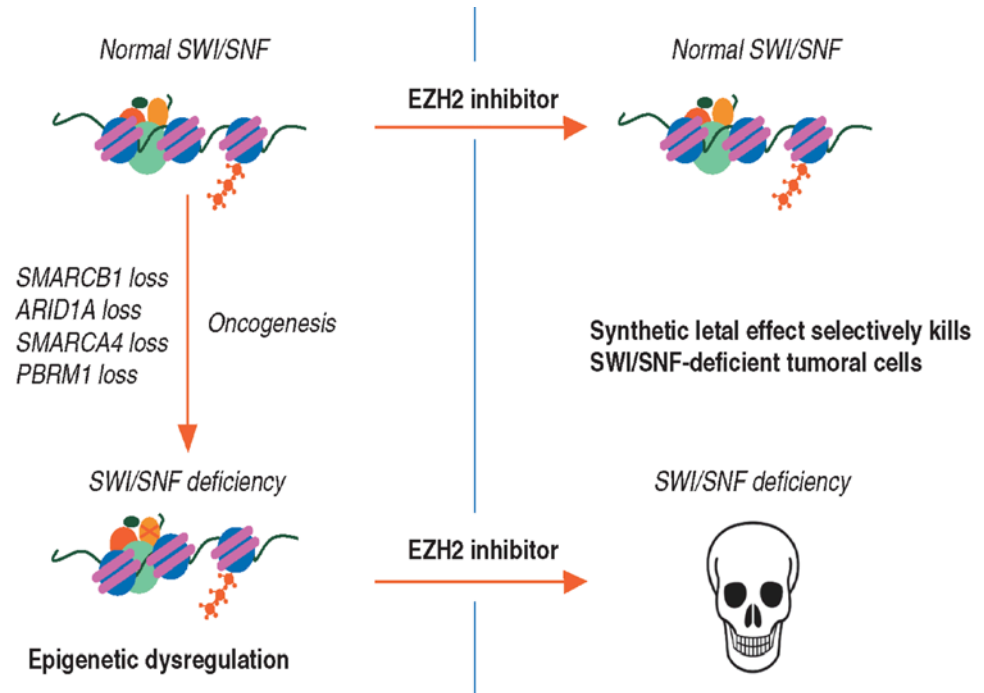
Case Study #3: Targeted therapy

MTB Case Study: Targeted Therapy

A 12 y/o boy with metastatic chordoma



February 2016



SOMATIC ALTERATIONS				
VARIANT	TRANSCRIPT ID	CLASSIFICATION	COVERAGE	MUTANT ALLELE FREQUENCY
SMARCB1 homozygous deletion	N/A	Pathogenic	N/A	N/A

Case Study #4: recurrent metastatic osteosarcoma with multiple potential therapeutic targets

Case Study #4: recurrent metastatic osteosarcoma with multiple potential therapeutic targets

- 18 yo F with metastatic osteosarcoma
- Treated with standard of care chemotherapy (cisplatin/doxorubicin/methotrexate)
- 99% necrosis at resection (consistent with a very good response)
- Developed metastatic disease in the lungs. Metastatectomy performed as clinically indicated. Viable tumor sent for sequencing.
- Second line chemotherapy (ifosfamide and etoposide), discontinued due to poor quality of life.

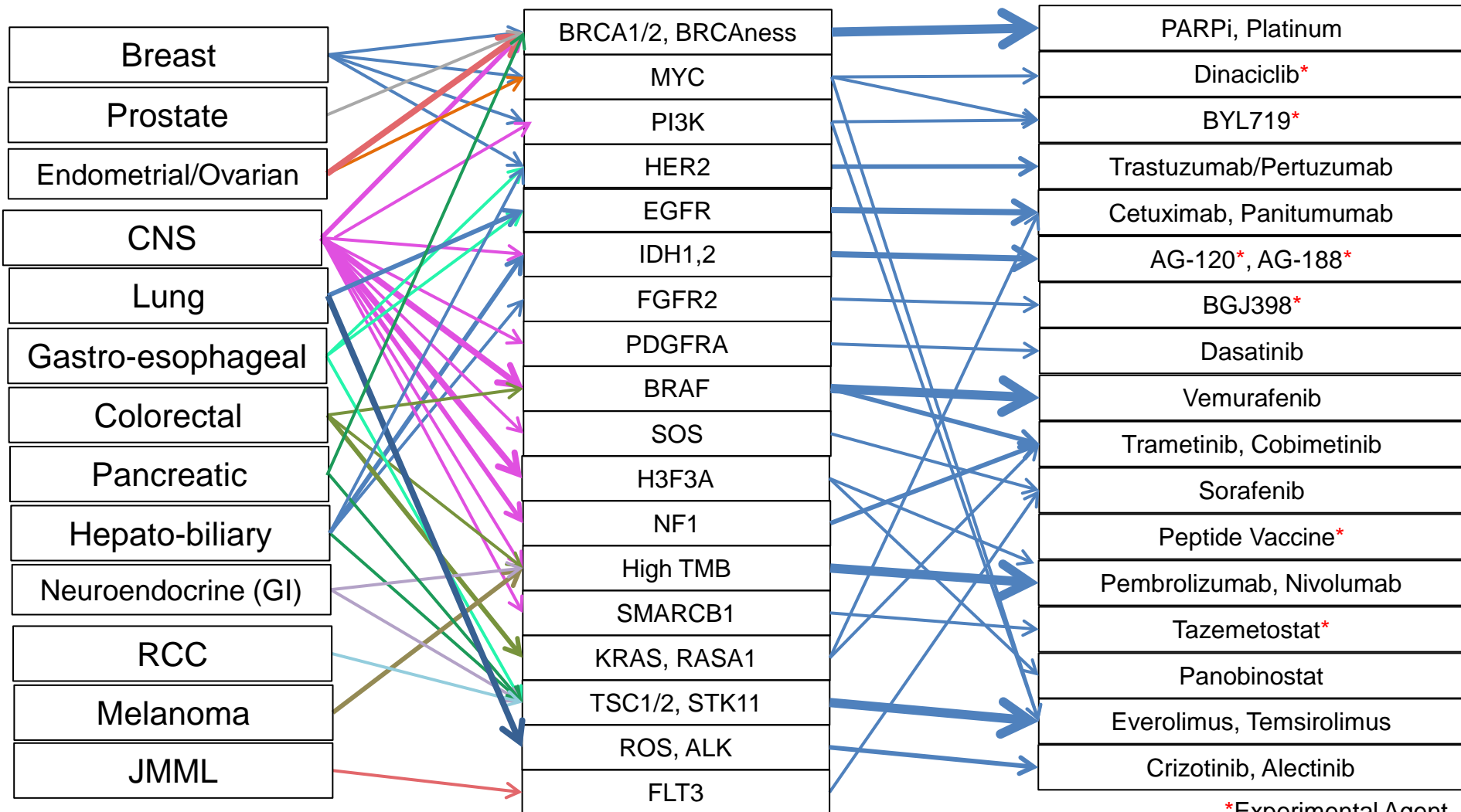
Case Study #4: recurrent metastatic osteosarcoma with multiple potential therapeutic targets

Pathogenic or Likely Pathogenic SOMATIC ALTERATIONS				
VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
CDK4 amplification	All	Pathogenic	~21.0x	N/A
MYC amplification	All	Pathogenic	~27.0x	N/A
PTEN deep deletion	All	Pathogenic	N/A	N/A
TP53 intron 1 structural variant	All	Pathogenic	537	N/A
MAP2K4 deep deletion	All	Likely Pathogenic	N/A	N/A

Multiple genes identified, consistent with recent work indicating these are common Copy number gained drivers in osteosarcoma (Sayles and Breese, Cancer Discovery 2019)

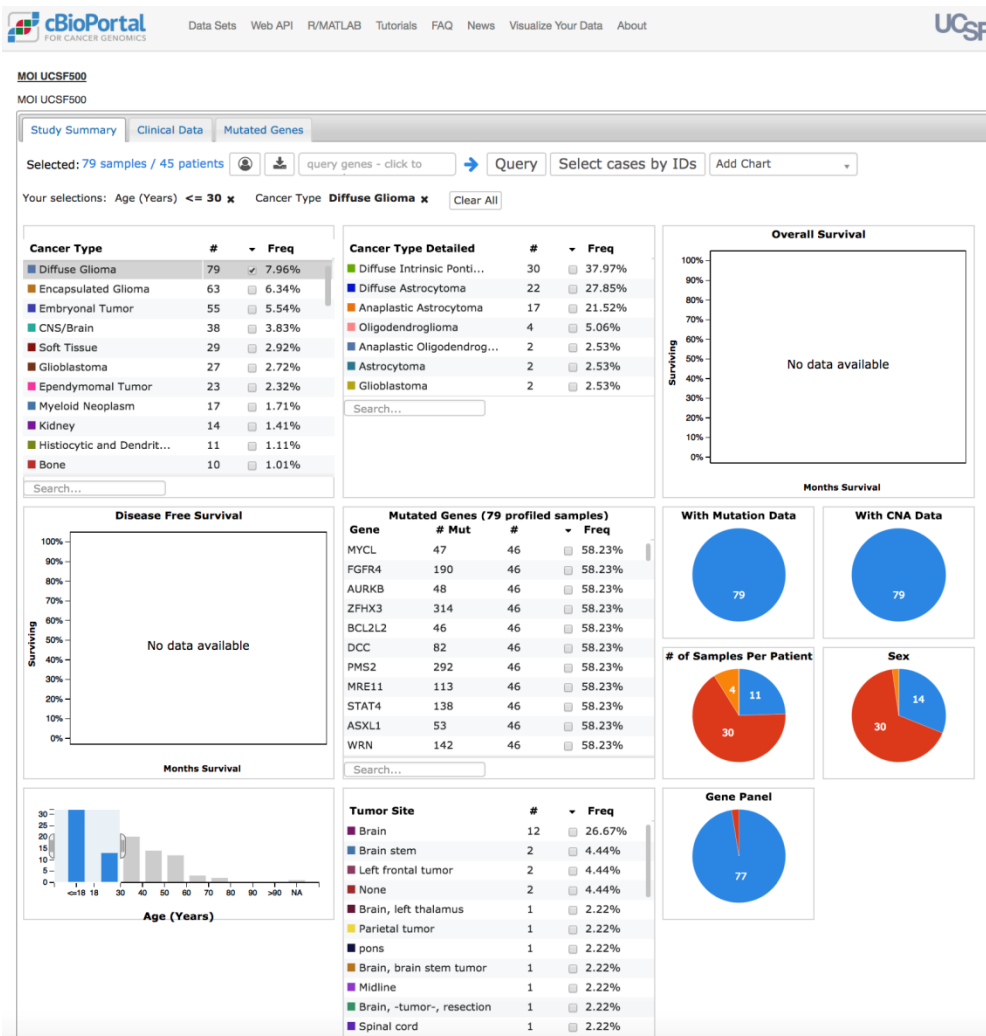
Patient currently on treatment with CDK4 inhibitor

Matching Disease-Gene-Drug



*Experimental Agent

Cbioportal: Disease-specific data exploration



Summary 79 Diffuse Gliomas

Cbioportal: Cross-disease gene centric analysis

CbioPortal FOR CANCER GENOMICS Data Sets Web API R/MATLAB Tutorials FAQ News Visualize Your Data About UCSF

MOI UCSF500 All cases in study (3265 samples) / 1 Genes Gene Set / Pathway is altered in 1240 (38%) of queried samples

OncoPrint Cancer Types Summary Plots Mutations Enrichments Network Download Bookmark

BRAF

BRAF
UniProt: BRAF_HUMAN
Transcript: ENST00000289602
Somatic Mutation Frequency: 38.0% **i**

136 Missense 1492 Truncating
10 Inframe 0 Other

View 3D Structure

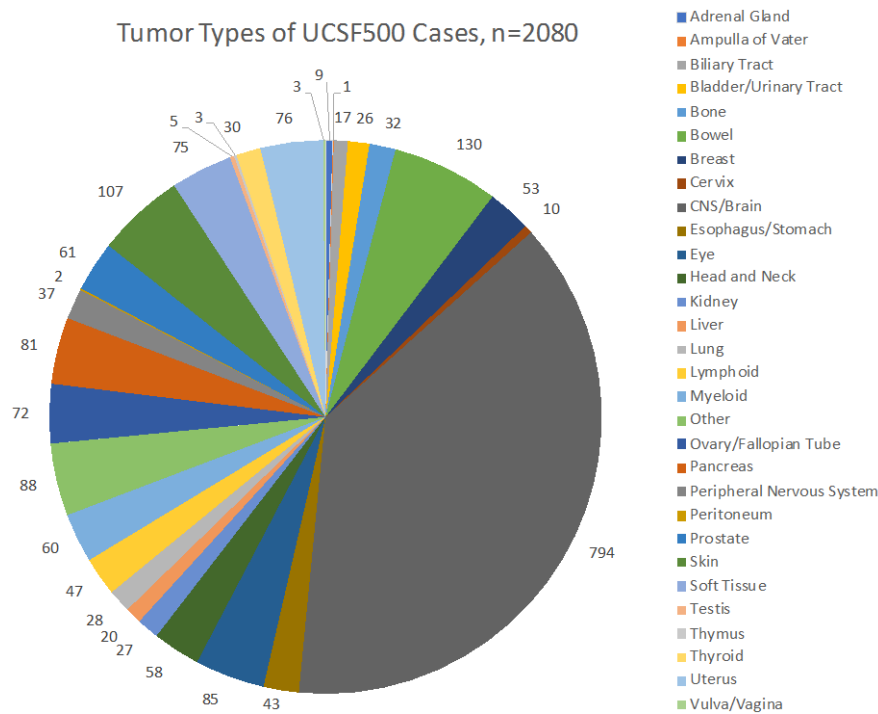
1638 Mutations: includes 321 duplicate mutations in patients with multiple samples (page 1 of 66)

Sample ID	Cancer Type	Protein Change	Annotation ▼	Mutation Type	COSMIC	Allele Freq (T)	# Mut in Sample
CGP-3665	Cutaneous Melanoma	V600E		Missense	23294		
CGP-6520	Cutaneous Melanoma	V600E		Missense	23294		
CGP-5005	Cutaneous Melanoma	V600E		Missense	23294	0.16	
CGP-4524	Acral Melanoma	V600E		Missense	23294		
CGP-3266	Anaplastic Thyroid Cancer	V600E		Missense	23294	0.34	
CGP-3981	Melanoma	V600R		Missense	23294	0.88	
CGP-3965	Melanoma	V600R		Missense	23294	0.62	
CGP-6100	Cutaneous Melanoma	V600K		Missense	23294	0.00	
CGP-4434	Acute Myeloid Leukemia	V600E		Missense	23294	0.00	
CGP-4438	Anaplastic Pleomorphic Xantho...	V600E		Missense	23294		
CGP-2260	Encapsulated Glioma	V600E		Missense	23294		
CGP-4525	Anaplastic Pleomorphic Xantho...	V600E		Missense	23294	0.32	
CGP-3156	Desmoplastic Infantile Ganglio...	V600E		Missense	23294		
CGP-2715	Anaplastic Pleomorphic Xantho...	V600E		Missense	23294		
CGP-4763	Ganglioglioma	V600E		Missense	23294		
CGP-6877	Mixed Cancer Types	V600E		Missense	23294		
CGP-3542	Glioblastoma	V600E		Missense	23294	0.38	
CGP-3543	Glioblastoma Multiforme	V600E		Missense	23294	0.00	
CGP-5584	Pleomorphic Xanthoastrocytoma	V600E		Missense	23294	0.40	
CGP-5677	Diffuse Glioma	V600E		Missense	23294	0.30	
CGP-4844	Oligodendroglioma	V600E		Missense	23294	0.20	
CGP-5064	Ganglioglioma	V600E		Missense	23294	0.37	
CGP-4238	Anaplastic Pleomorphic Xantho...	V600E		Missense	23294		
CGP-2312	Anaplastic Astrocytoma	V600E		Missense	23294		
CGP-6198	Piloicytic Astrocytoma	V600E		Missense	23294		

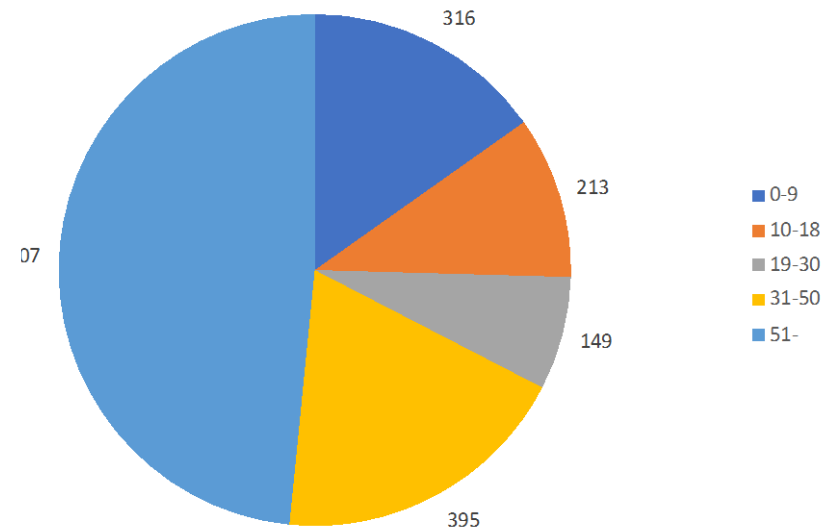
Showing 1-25 of 1638 Mutations: includes 321 duplicate mutations in patients with multiple samples Show more

UCSF500 demographics

Tumor Types of UCSF500 Cases, n=2080

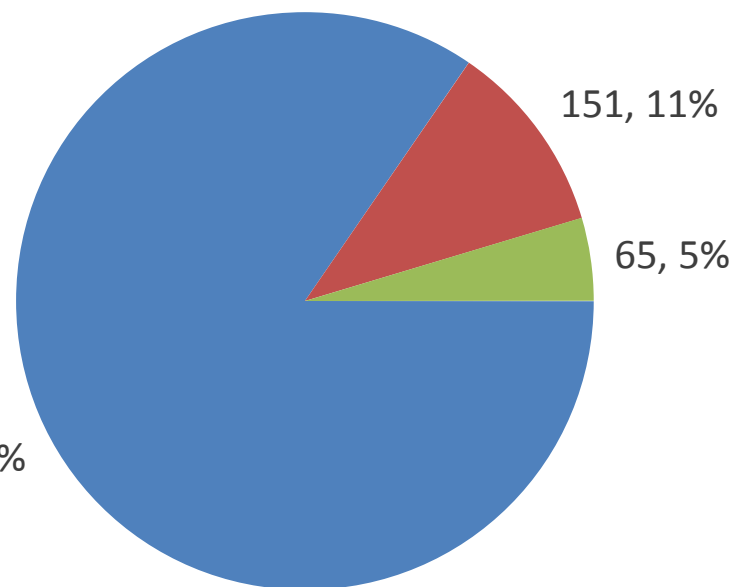


Patient Age of UCSF500 Cases, n=2080

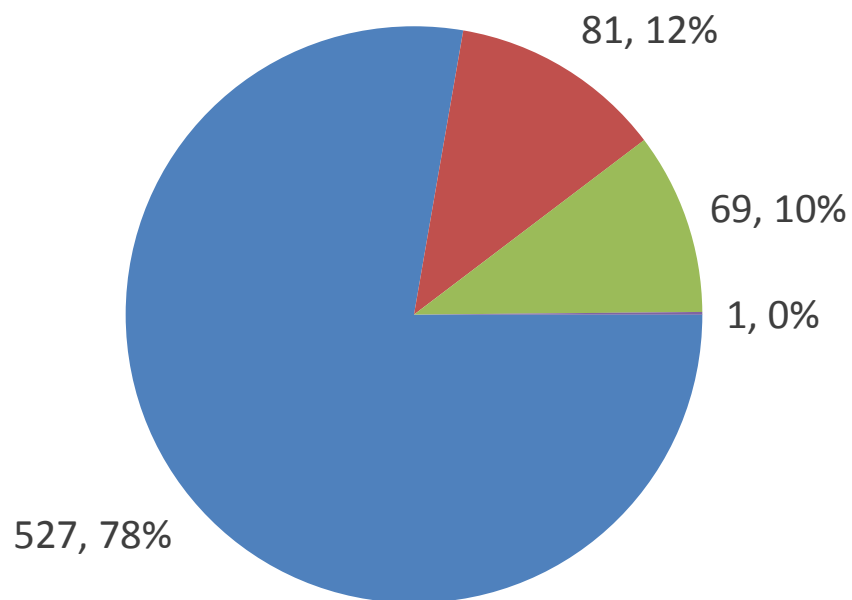


UCSF50: informative vs non-informative cases

Adult Cases (n=1402)



Pediatric Cases (n=678)

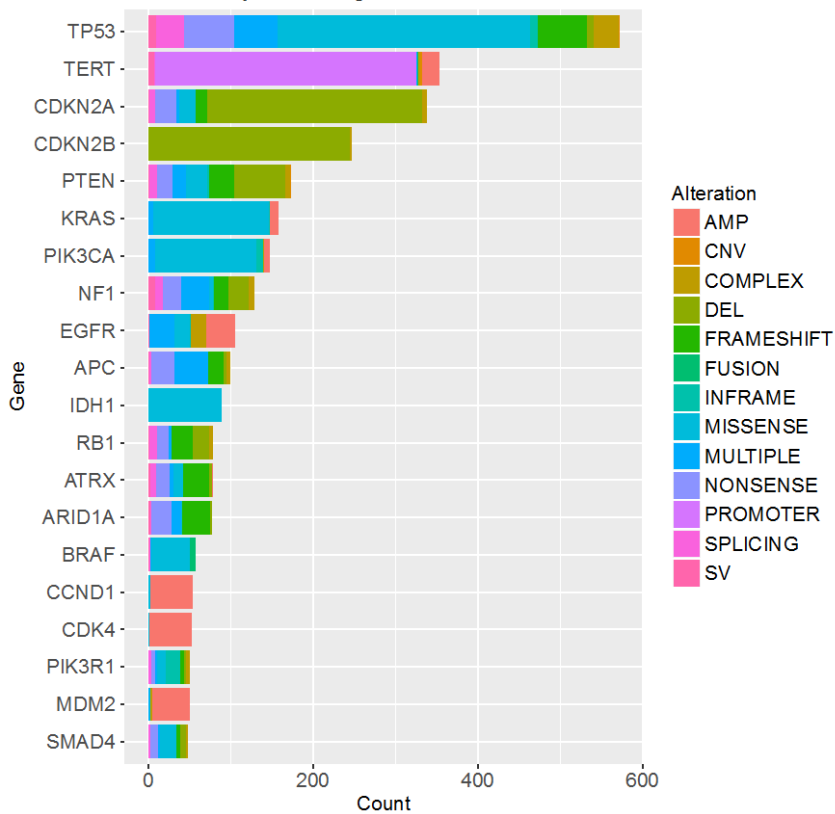


■ Somatic Only ■ Somatic and Germline ■ No Pathogenic Variants Detected ■ Germline Only

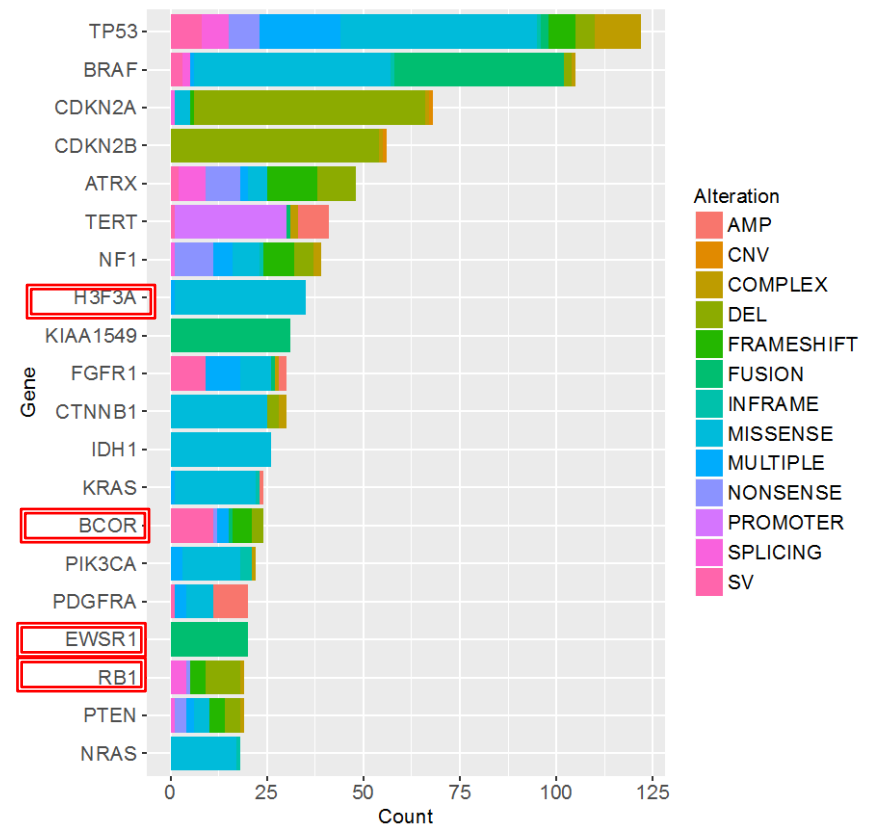
90-95% of samples had an informative assay (likely pathogenic or pathogenic alteration somatic alteration AND/OR a germline alteration found).

Most commonly altered somatic genes adult vs. pediatric

20 most commonly mutated genes in tumor – Adult UCSF500 cases



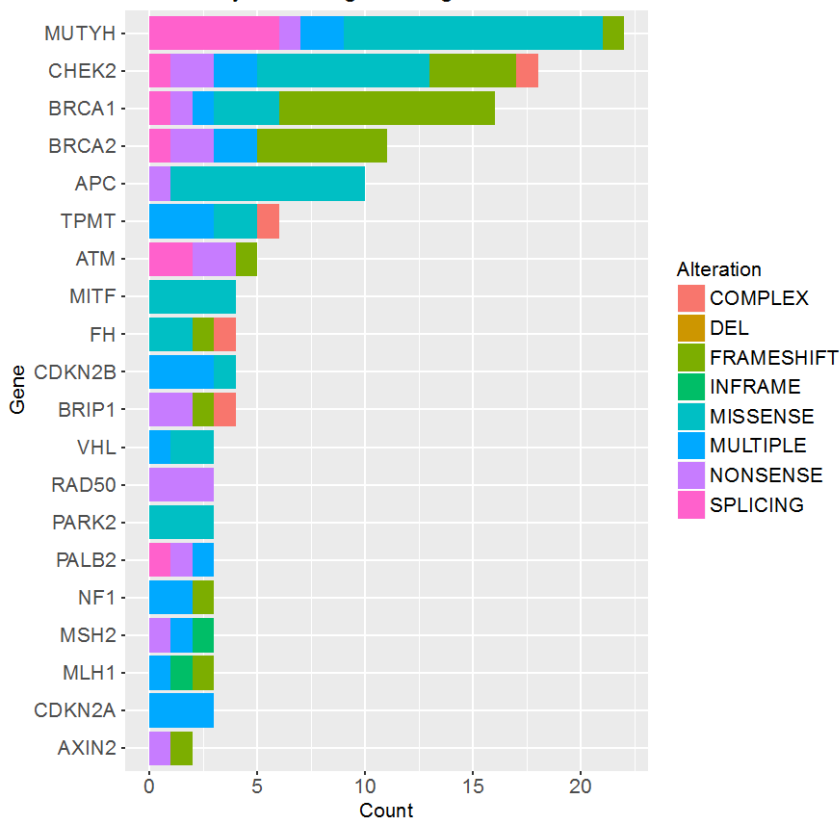
20 most commonly mutated genes in tumor – UCSF500 pediatric cases



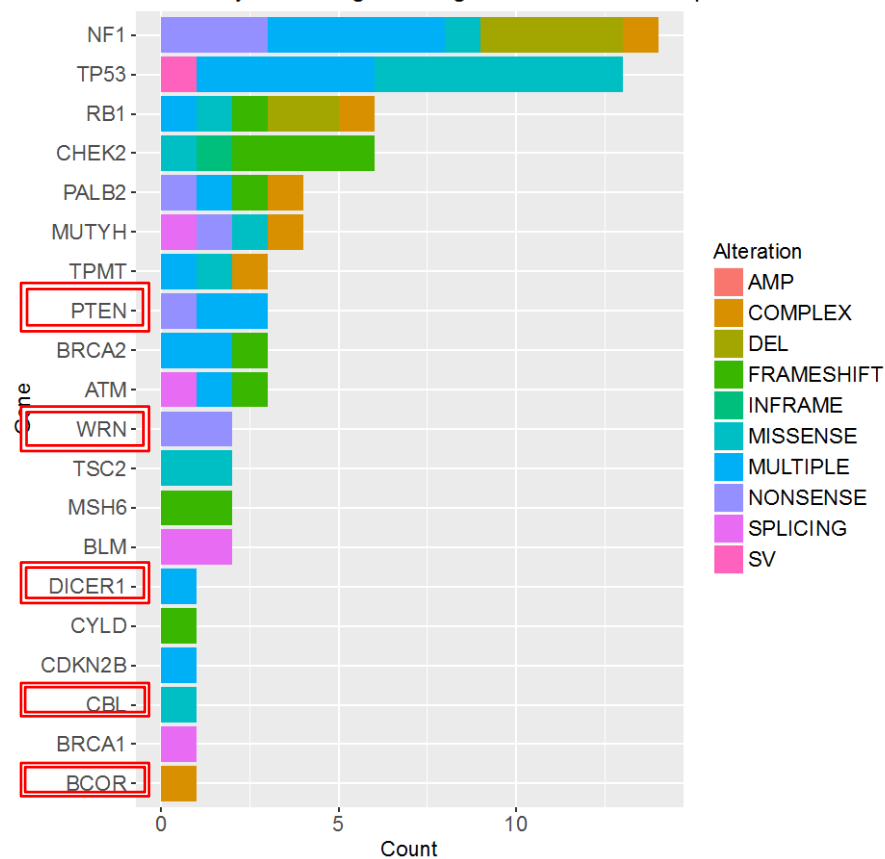
 =not seen in adult

Most commonly altered germline genes adult vs. pediatric

20 most commonly mutated genes in germline – Adult UCSF500 cases

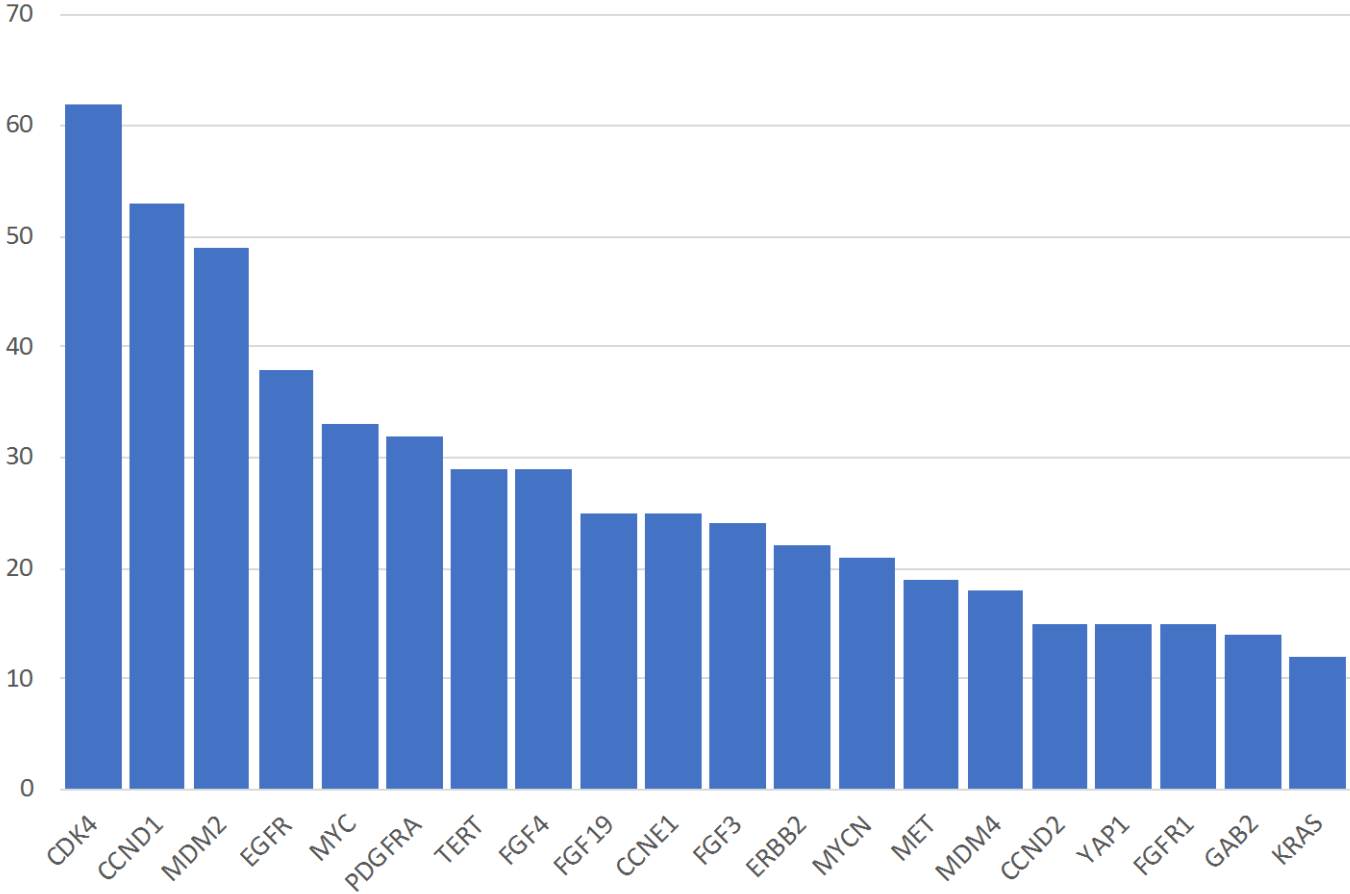


20 most commonly mutated genes in germline – UCSF500 pediatric cases



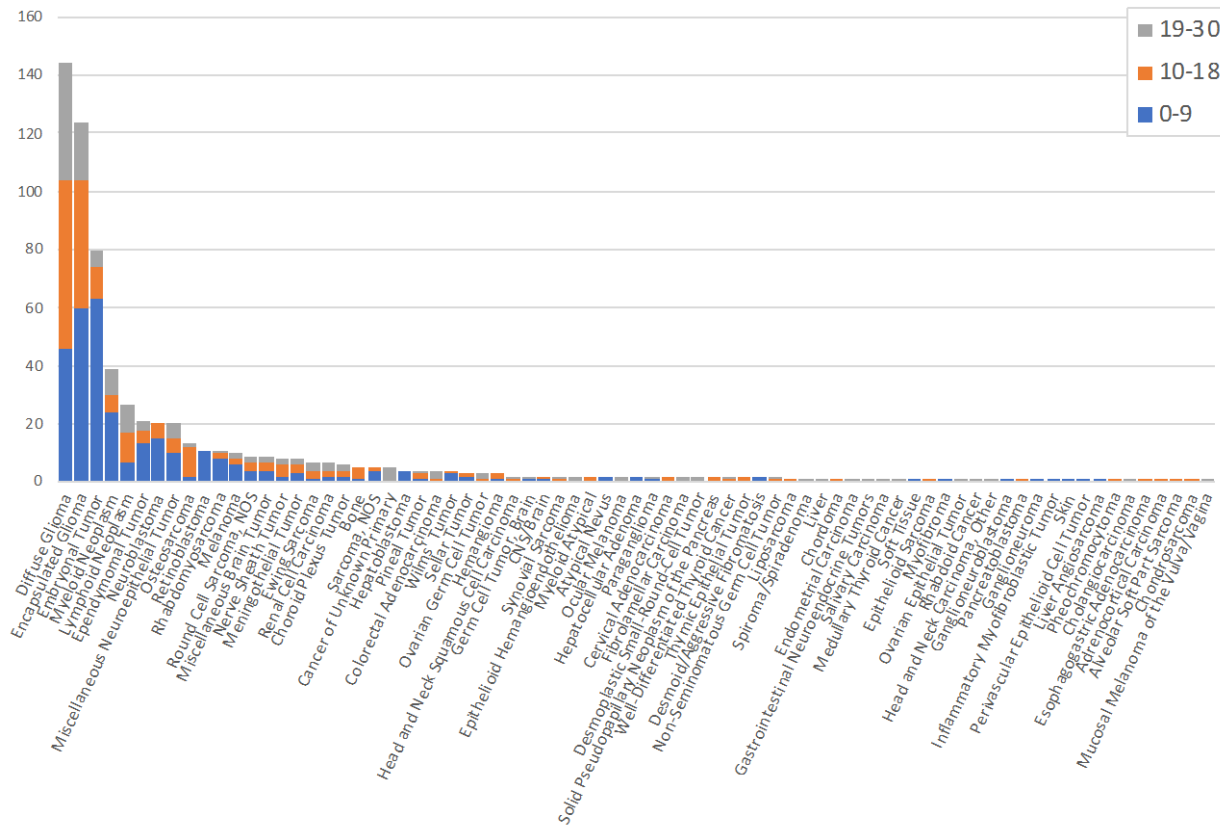
Most common focal copy number alterations in UCSF500

20 most common focal amplifications



Long “Tail” of diagnosis in pediatric cancers

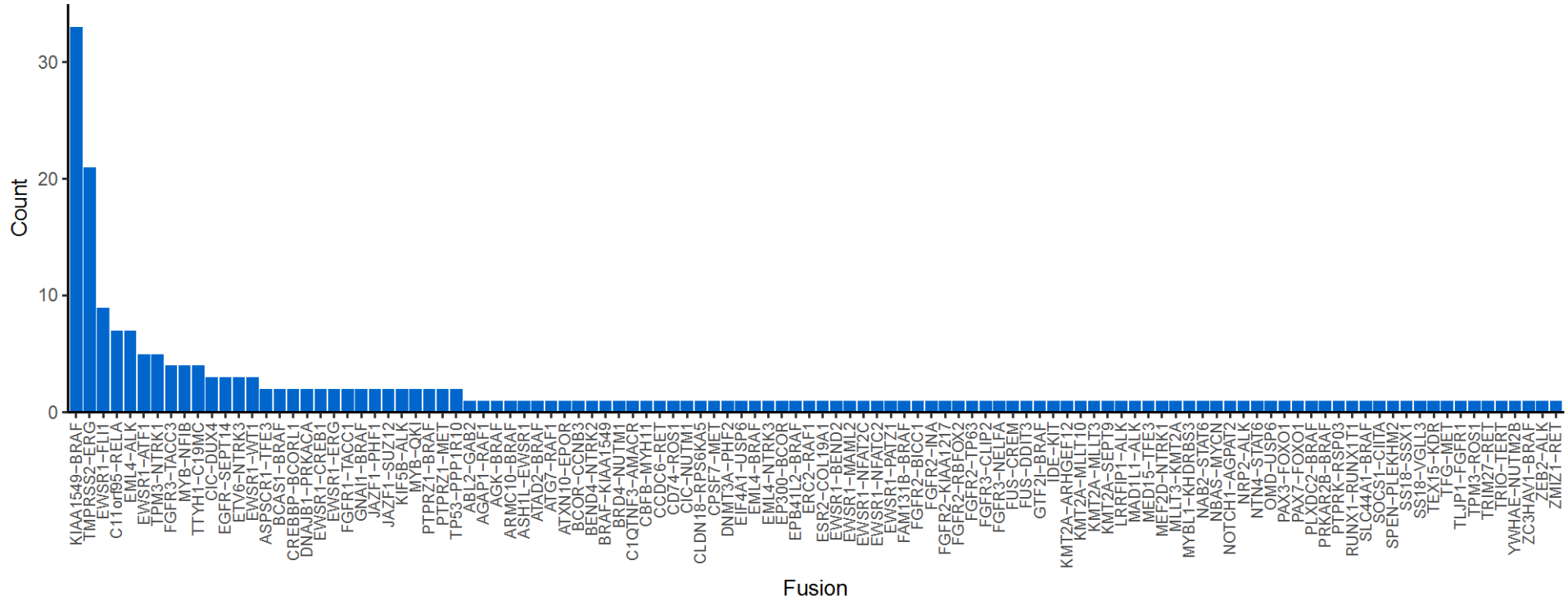
Tumor Types of Pediatric UCSF500 Cases, n=678



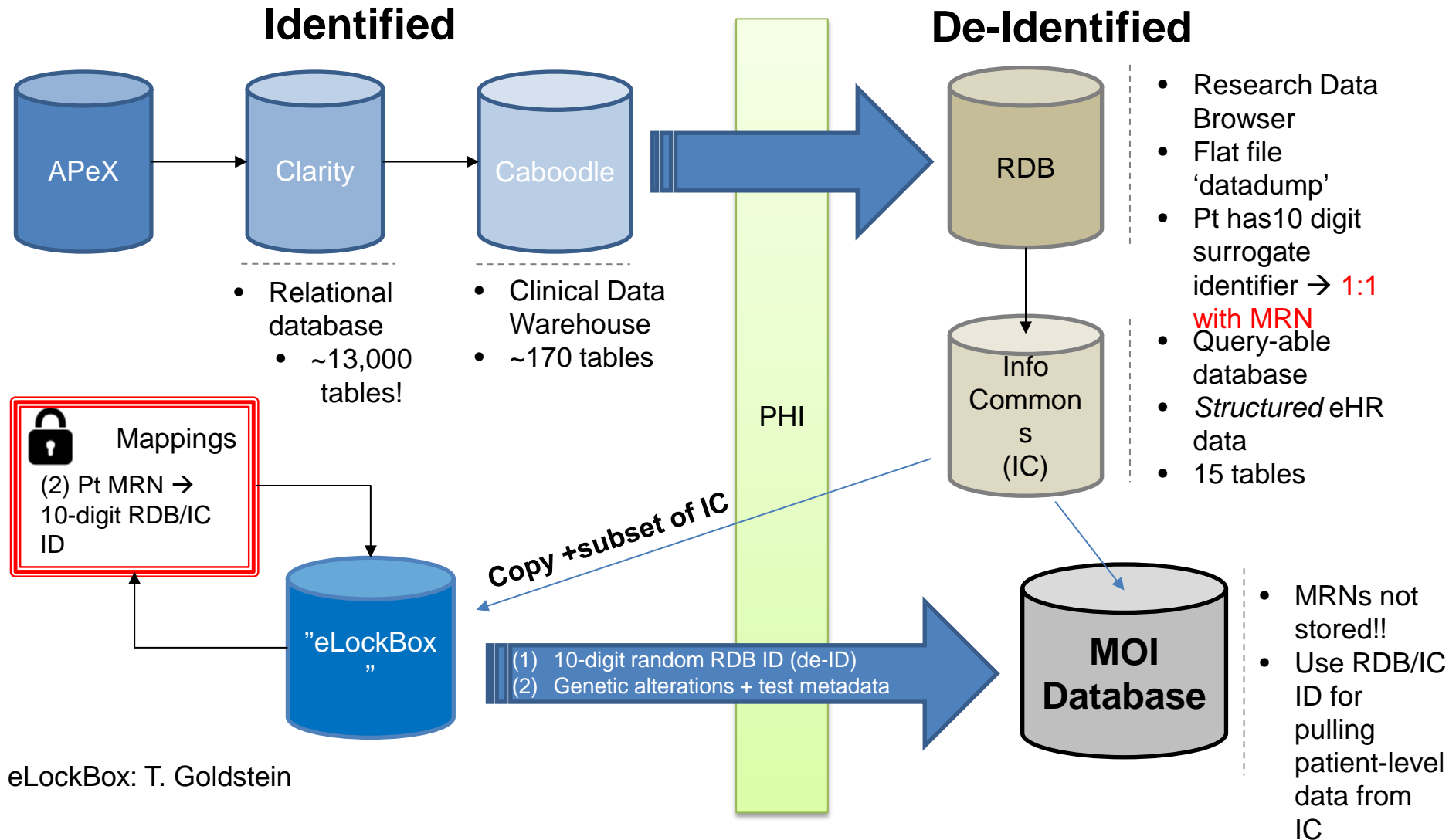
TOTAL CASES	539
TOTAL CASES WITH GERMLINE FINDINGS	70
NUMBER OF DIAGNOSIS FOUND IN LESS THAN 5% OF CASES	60

Long "Tail" of fusion genes

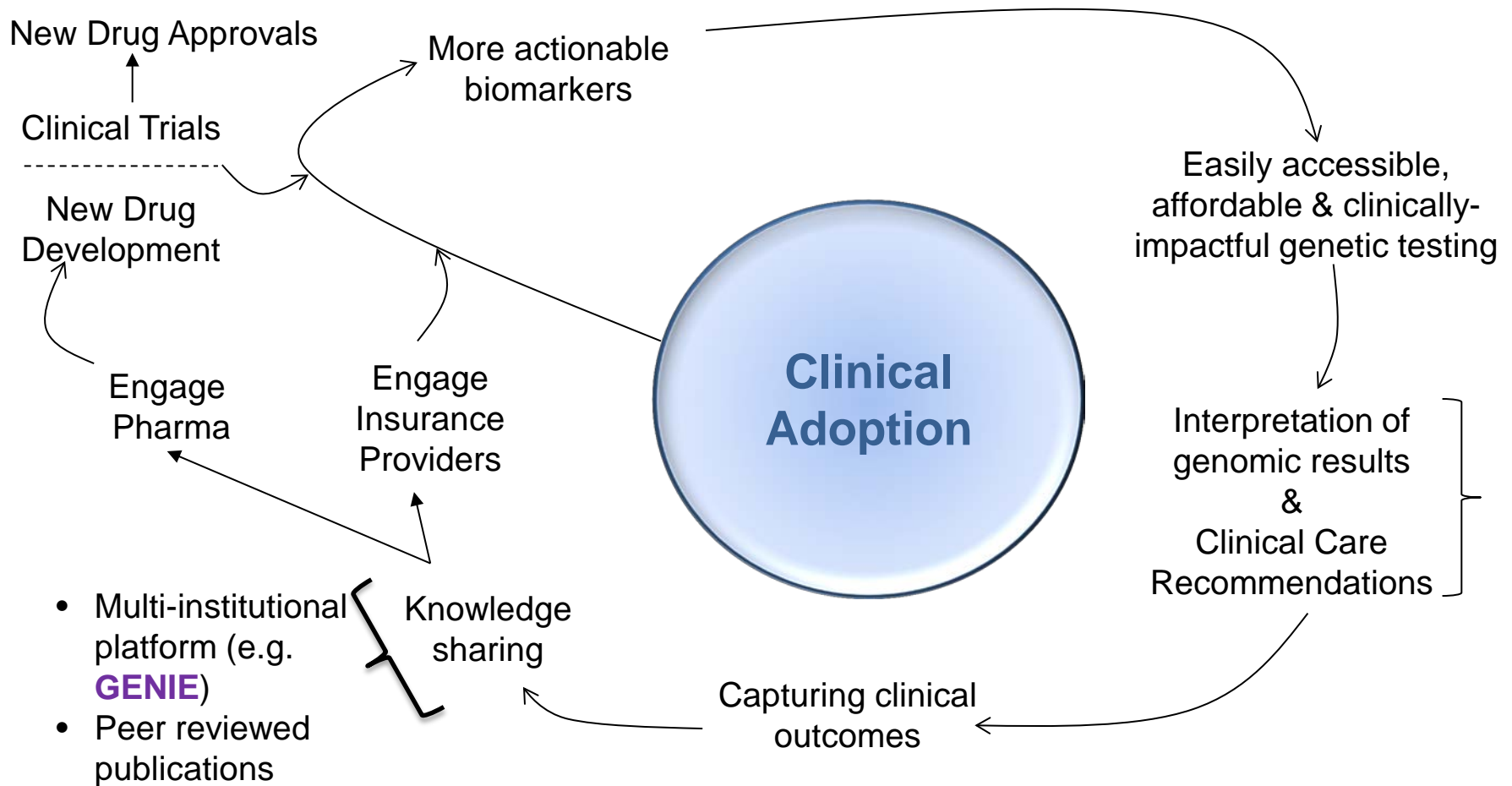
Fusions in UCSF500 Cases



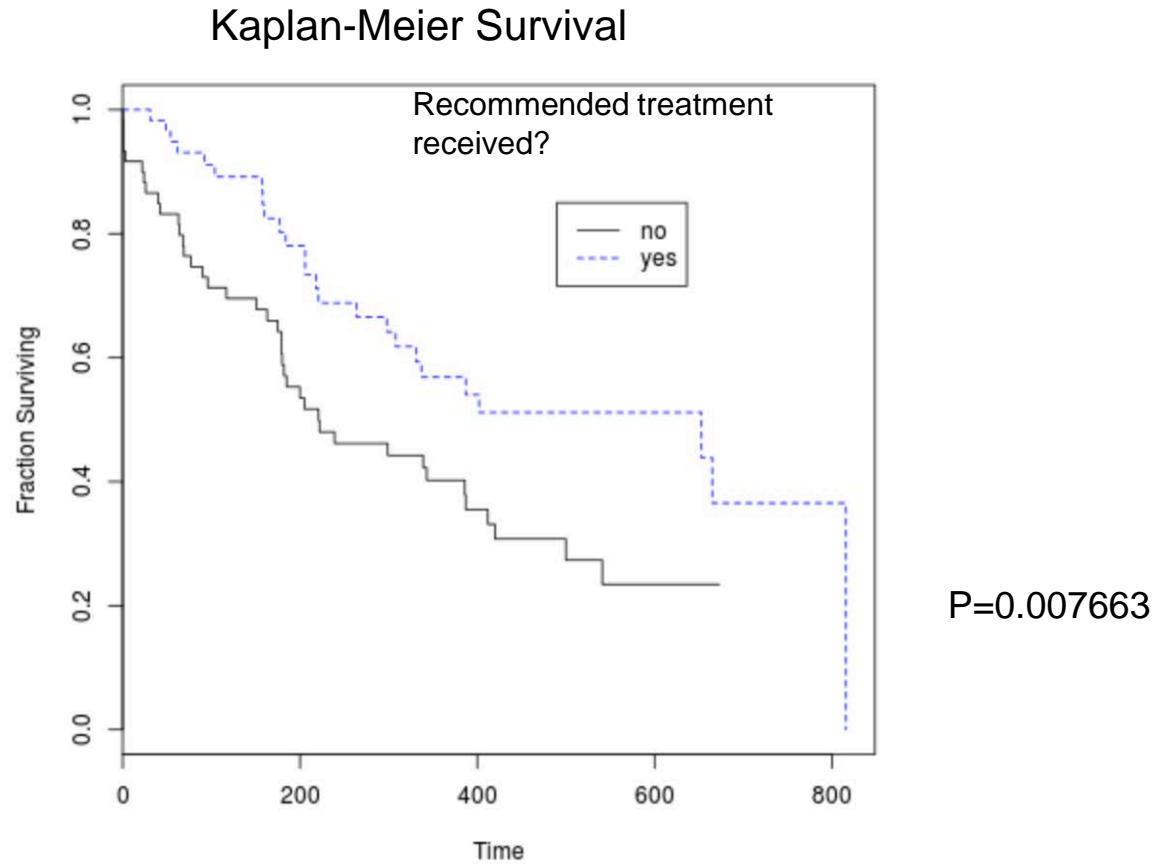
Annotating genomic data using the EHR



Precision Oncology Flywheel



Does precision medicine lead to improved outcomes?



Project GENIE



International pancancer registry built through data sharing

Driven by openness, transparency, and inclusion



- GOAL: improve clinical decision making
 - Linking clinical genotype to clinical outcomes
-

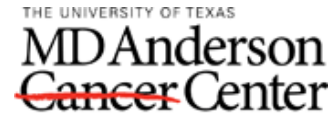


- Eight founding participants, now 19
 - North America & Europe
 - Plans for future expansion
-



- Sponsored research
- Collaborative projects

Project GENIE: participants



Key challenges

- Building a knowledge base base on:
 - external data
 - analysis of internal data and prior experience
- Linking to clinical trials
- Clinical annotation of genomic results by data extraction from EMR.
- Determining clinical utility and better definition of real-world barriers to utility

Summary

- The UCSF500 assay can detect a wide range of clinically relevant alterations that can modify therapy, refine diagnosis and identify inherited cancer predispositions.
- UCSF500 is unique in its coverage of both adult and pediatric alterations and paired germline/somatic analysis.
- Emerging opportunities for research in defining best practices to maximize utility of genomic testing.
- Data sharing through GENIE will increase opportunities for real world analysis of cancer precision medicine.

Acknowledgements

Molecular Oncology Initiative/CGL

Michelle Turski
Ted Goldstein
Nhani Tran
Jessica Van Ziffle
Carlos Espinoza
Courtney Onodera
J.P. Grenert
David Solomon

Cassie Kline
Elliot Stieglitz
Mark Moasser
Eric Collisson
Boris Bastian
Iwei Yeh
Jennifer Grabowski
Amy Blanco